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(54) Title: PYRAZOLOPYRIDINES AND ANALOGS THEREOF

(57) Abstract: Pyrazolopyridin-4-amines, pyrazoloquinolin-4-amines, pyrazolonaphthyridin-4-amines, and 6,7,8,9-tetrahydropyrazoloquinolin-4-amines, pharmaceutical compositions containing the compounds, intermediates, and methods of use of these compounds as immunomodulators, for inducing or inhibiting cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases, are disclosed.

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PYRAZOLOPYRIDINES AND ANALOGS THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Application Serial Nos. 60/508352, filed October 3, 2003, 60/554680, filed March 19, 2004, and 60/603303, filed August 20, 2004, all of which are incorporated herein by reference.

BACKGROUND

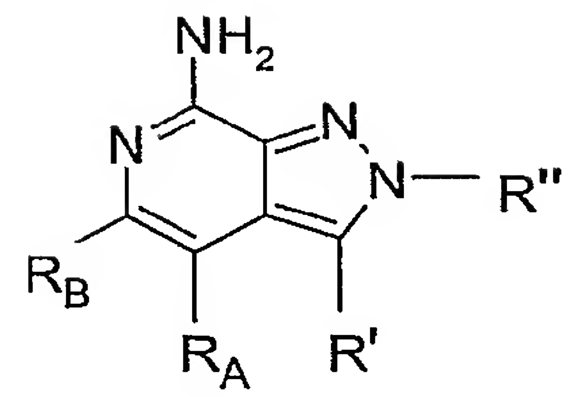
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*]quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*] pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders.

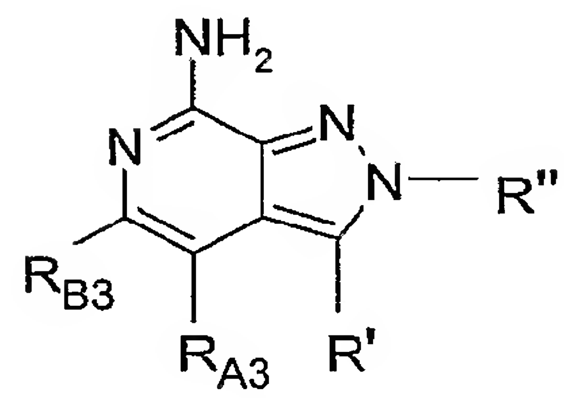
But despite important progress in the effort to find immunomodulating compounds, there is still a scientific and medical need for compounds that have an ability to modulate the immune response, by induction or inhibition of cytokine biosynthesis or other mechanisms.

SUMMARY OF THE INVENTION

A new class of compounds useful for modulating cytokine biosynthesis has now been found. In one aspect, the present invention provides such compounds, which are of the Formulas I and Ia:

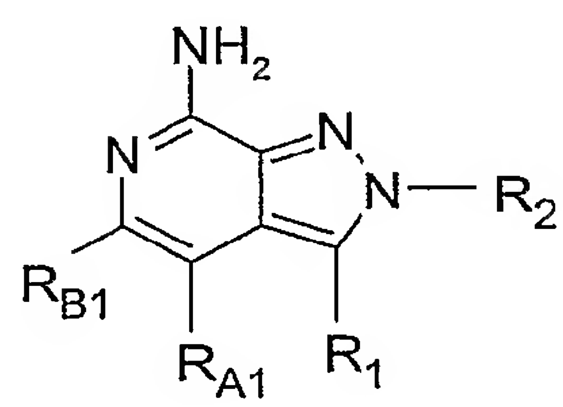


I

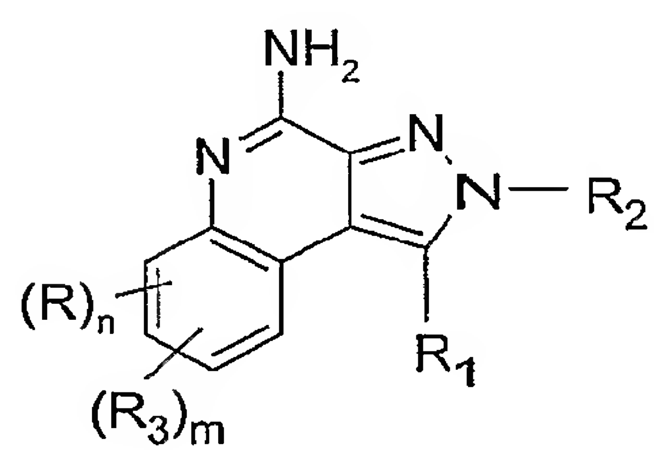


Ia

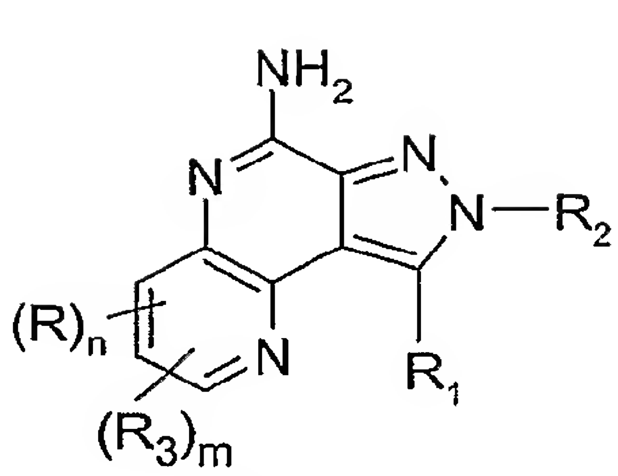
and more specifically the following compounds of the Formulas II, III, IV, V, VI, VII, VIII, and IX:



II



III



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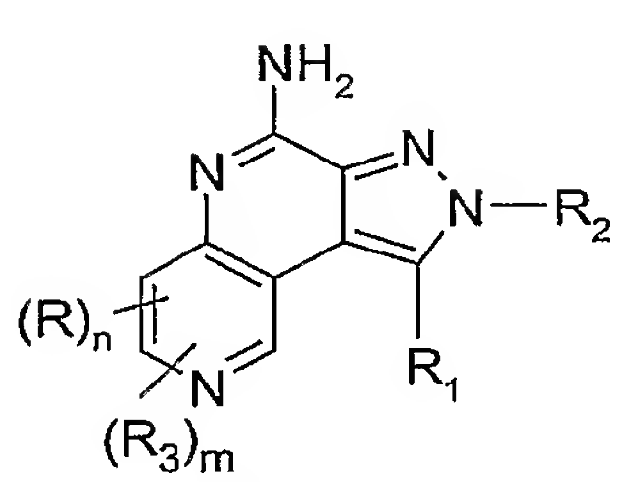
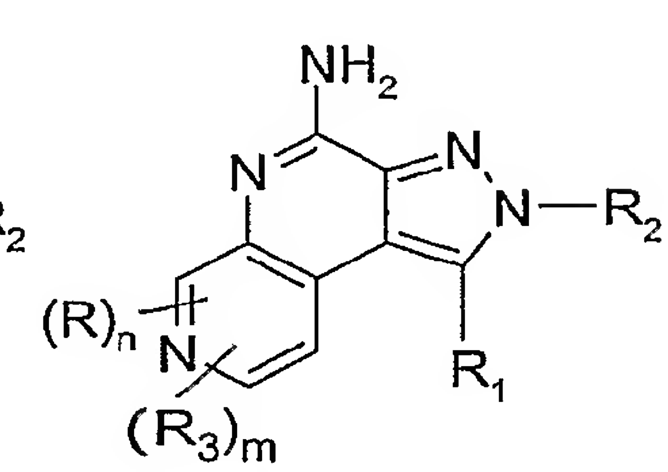
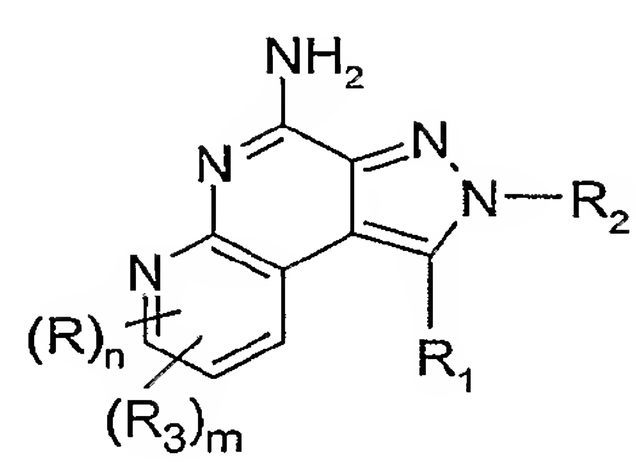


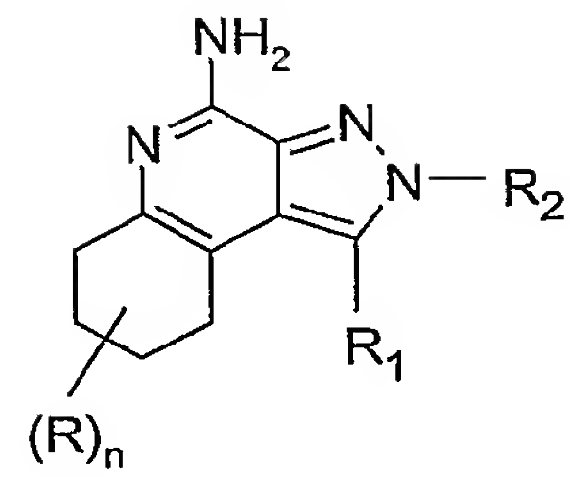
V



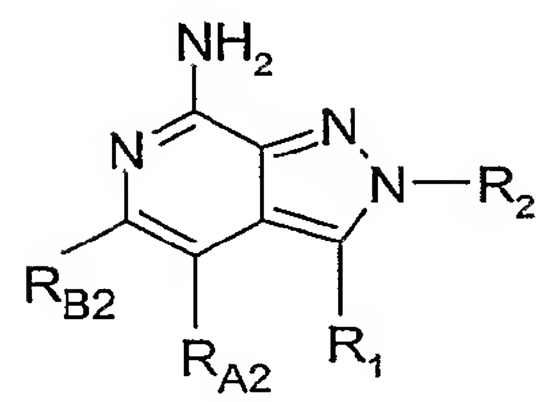
VI



VII



VIII



IX

wherein R_A, R_B, R', R'', R_{A1}, R_{B1}, R_1, R_2, R_3, R, R_{A2}, R_{B2}, R_{A3}, R_{B3}, n, and m are as defined below; and pharmaceutically acceptable salts thereof.

The compounds of Formulas I, Ia, II, III, IV, V, VI, VII, VIII, and IX are useful as immune response modifiers (IRMs) due to their ability to modulate cytokine biosynthesis (e.g., induce or inhibit the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. Compounds can be tested per the test procedures described in the Examples Section. Compounds can be tested for induction of cytokine biosynthesis by incubating human peripheral blood mononuclear cells (PBMC) in a culture with the compound(s) at a concentration range of 30 to 0.014 μM and analyzing for interferon (α) or tumor necrosis factor (α) in the culture supernatant. Compounds can be tested for inhibition of cytokine biosynthesis by incubating mouse macrophage cell line Raw 264.7 in a culture with the compound(s) at a single concentration of, for example, 5 μM and analyzing for tumor necrosis factor (α) in the culture supernatant. The ability to modulate cytokine biosynthesis, for example, induce the biosynthesis of one or more cytokines, makes the compounds useful for treating various conditions such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions that contain the immune response modifier compounds, and methods of modulating (e.g.,

inducing or inhibiting) cytokine biosynthesis in an animal, treating a viral disease in an animal, and treating a neoplastic disease in an animal, by administering an effective amount of one or more compounds of the Formulas I, Ia, II, III, IV, V, VI, VII, VIII, and/or IX and/or pharmaceutically acceptable salts thereof to the animal.

In another aspect, the invention provides methods of synthesizing compounds of the Formulas I, Ia, II, III, IV, V, VI, VII, VIII, and IX and intermediates useful in the synthesis of these compounds.

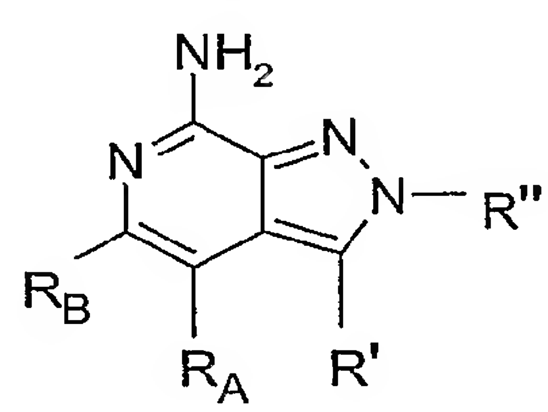
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

In one aspect, the present invention provides compounds of the formula (I):



I

wherein:

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R' and R'' are independently selected from the group consisting of hydrogen and non-interfering substitutents;

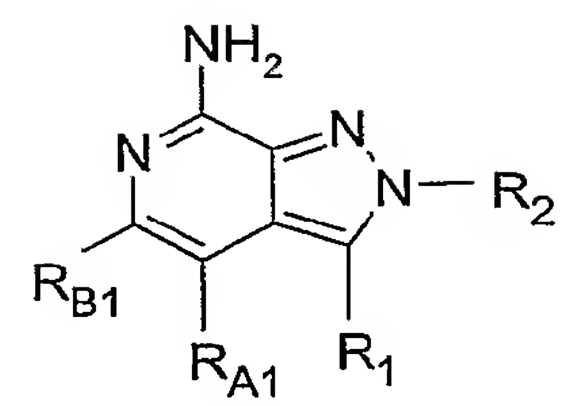
R''' is a non-interfering substituent; and

R_9 is selected from the group consisting of hydrogen and alkyl;

with the proviso that at least one of R_A, R_B, R', or R'' is other than hydrogen; and with the further proviso that when R_A and R_B form a benzene ring unsubstituted or substituted with chloro, and R' is hydrogen, then R'' is other than phenyl or phenyl substituted with methyl, methoxy, chloro, or fluoro;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides compounds of the formula (II):



II

wherein:

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

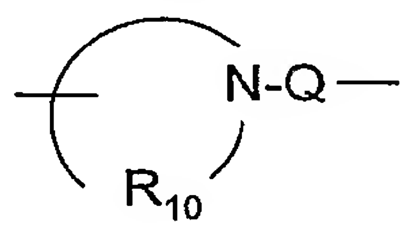
$-C(R_6)-N(OR_9)-$,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,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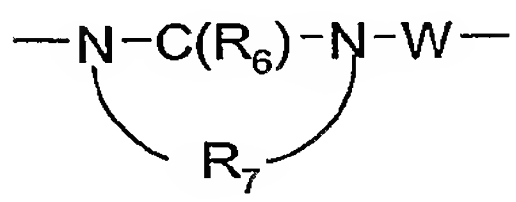
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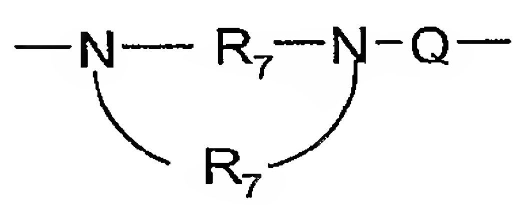
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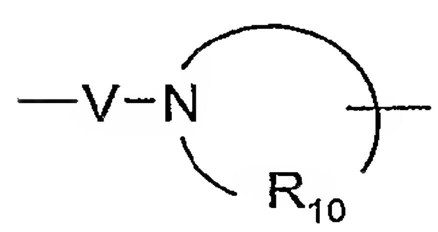
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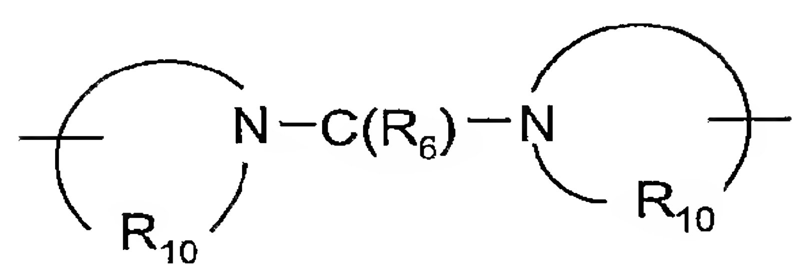
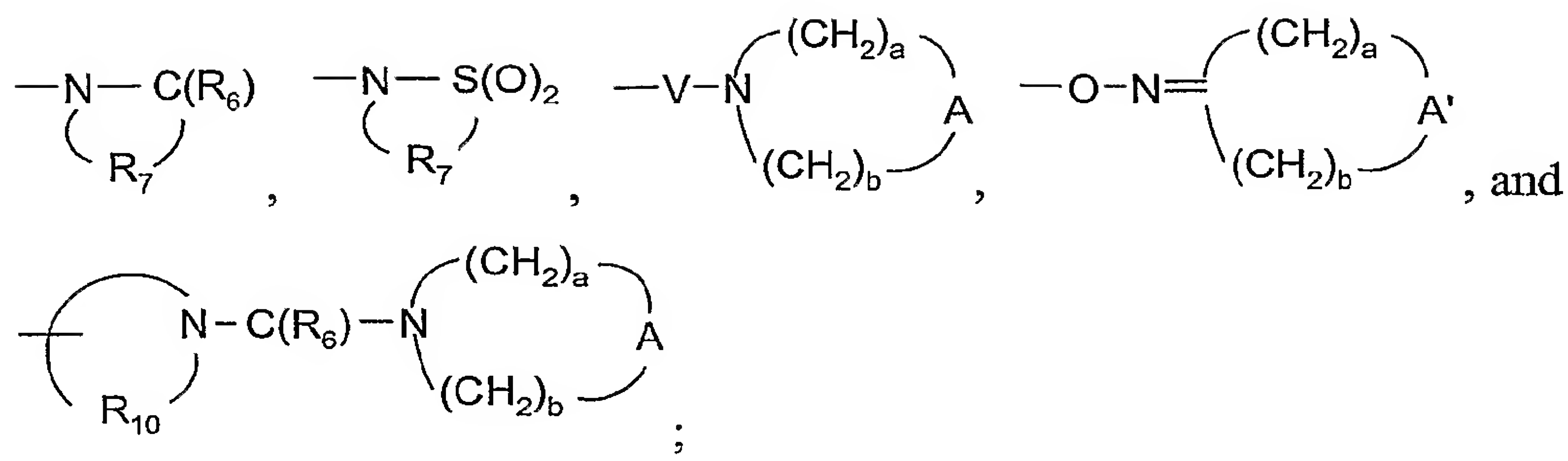

;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, and –N(R_4)-;

A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

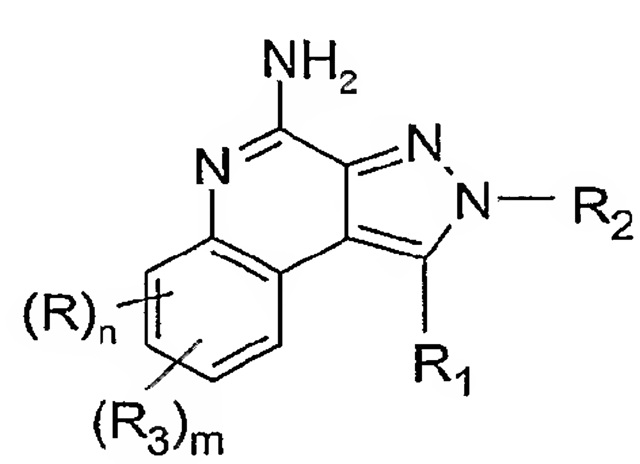
W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7;

with the proviso that at least one of R_{A1}, R_{B1}, R_1, or R_2 is other than hydrogen; and with the further proviso that when R_{A1} and R_{B1} form a fused benzene ring unsubstituted or substituted with chloro, and R_1 is hydrogen, then R_2 is other than phenyl or phenyl substituted with methyl, methoxy, chloro, or fluoro;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides compounds of the formula (III):



III

wherein:

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

n is 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

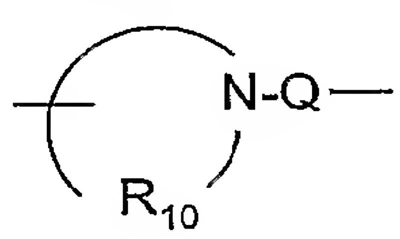
-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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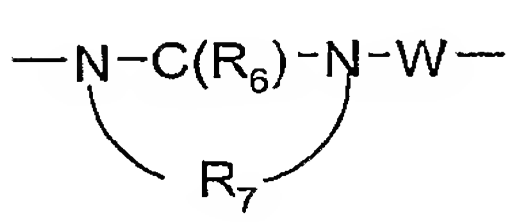

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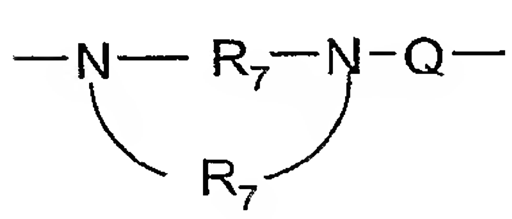

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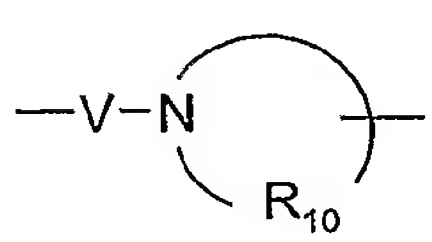

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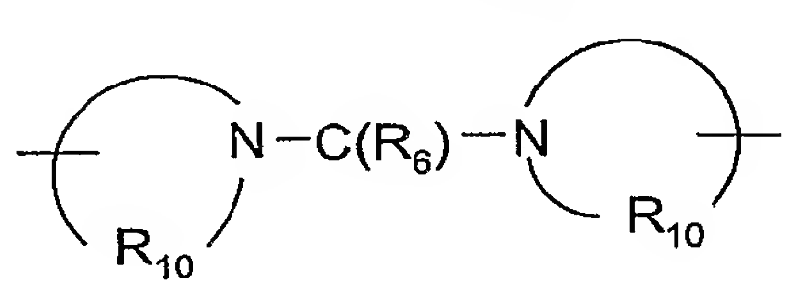


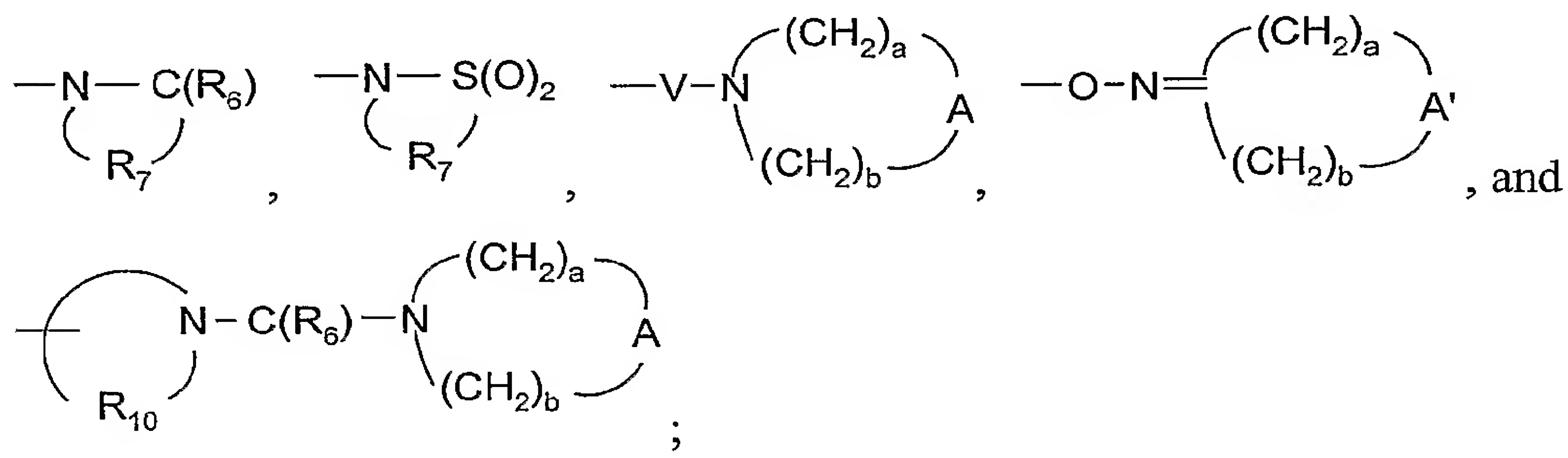
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, and –N(R_4)-;

A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

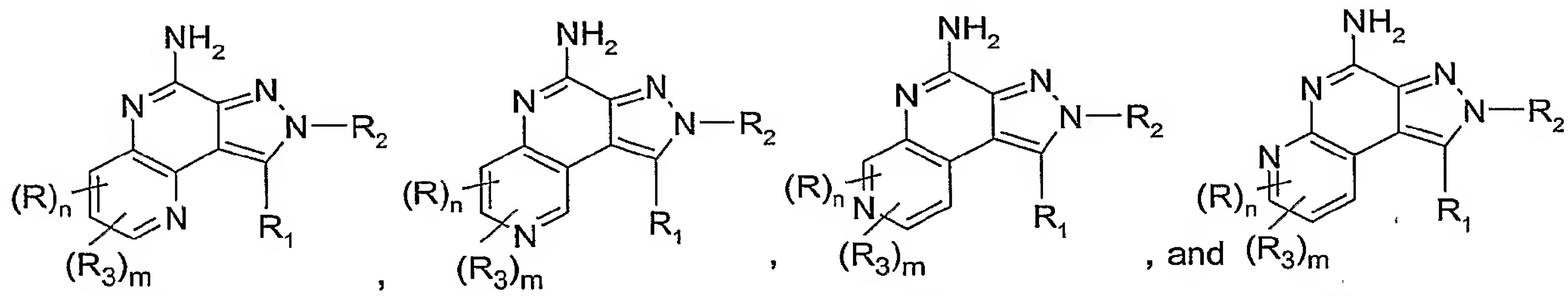
W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

with the proviso that when R_1 is hydrogen, m is 0, and R is chloro, then R_2 is other than phenyl or phenyl substituted with methyl, methoxy, chloro, or fluoro;

or a pharmaceutically acceptable salt thereof.

In other embodiments, the present invention provides compounds of the formulas (IV, V, VI, and VII):



IV V VI VII

wherein:

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X-R_4,

-Z-X-Y-R_4,

-Z-X-Y-X-Y-R_4, and

-Z-X-R_5;

n is 0 or 1;

m is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

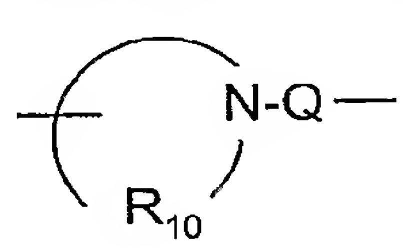
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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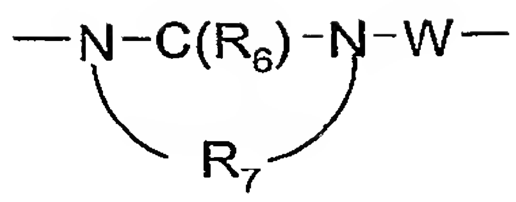

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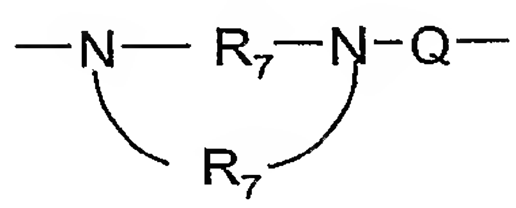

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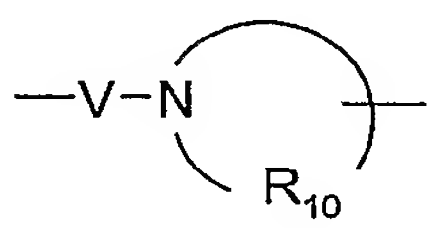

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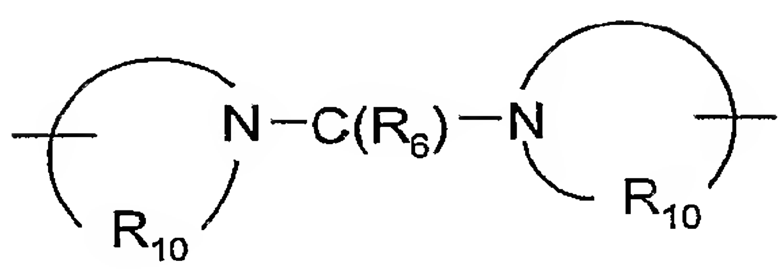
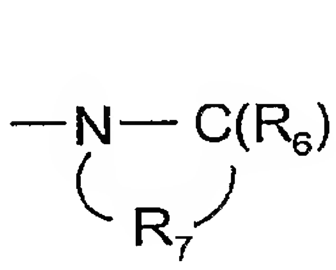


;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



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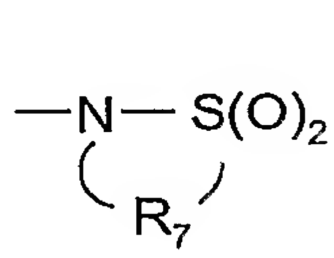

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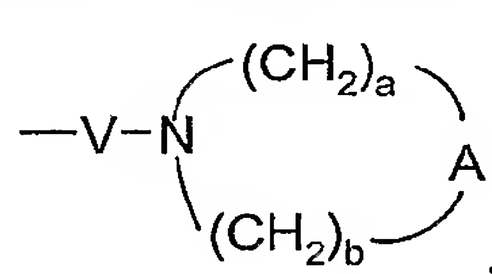

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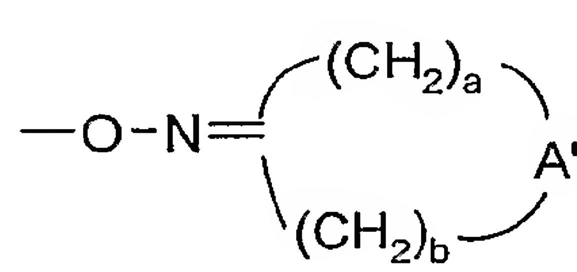

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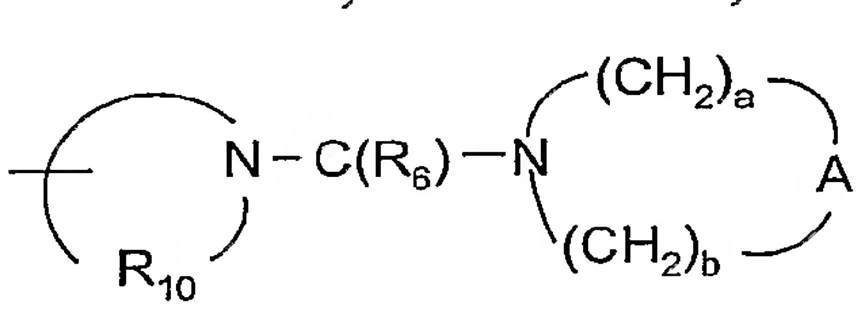


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

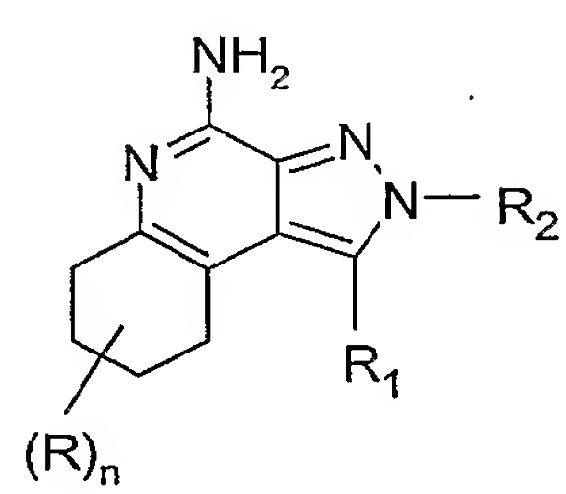
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides compounds of the formula (VIII):



VIII

wherein:

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

n is 0 to 4;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

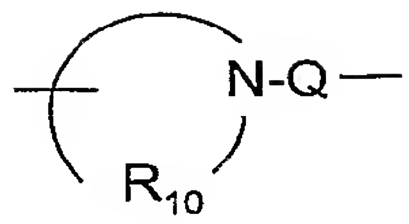
-C(R_6)-N(OR_9)-,

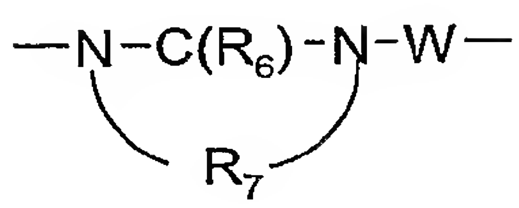
-O-N(R_8)-Q-,

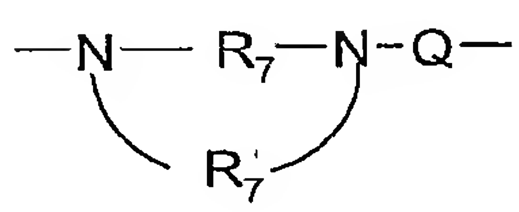
-O-N=C(R_4)-,

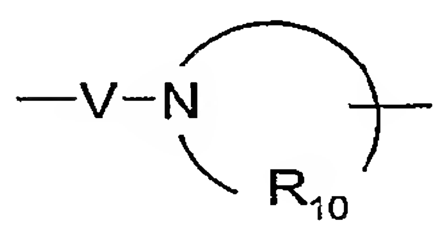
-C(=N-O-R_8)-,

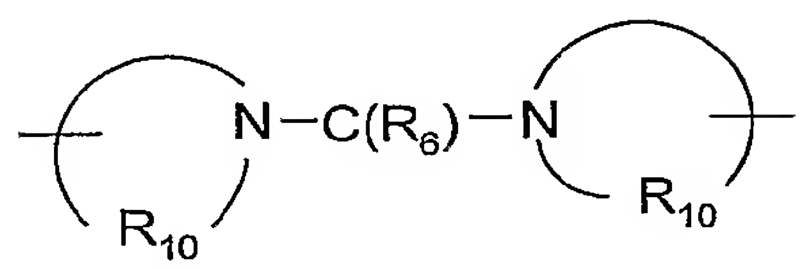
-CH(-N(-O-R_8)-Q-R_4)-,

,

,

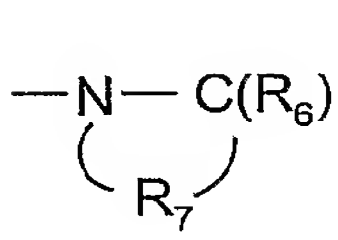
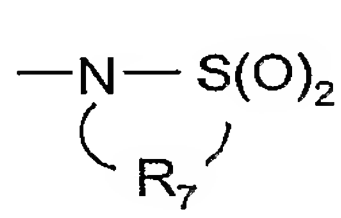
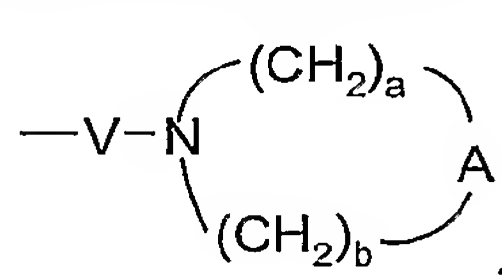
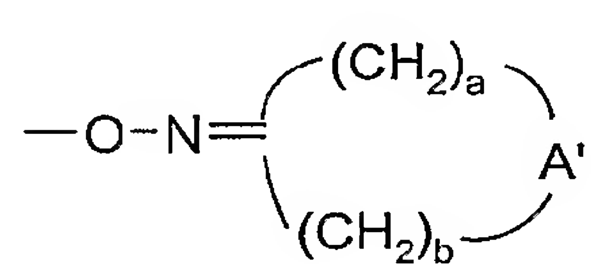
,

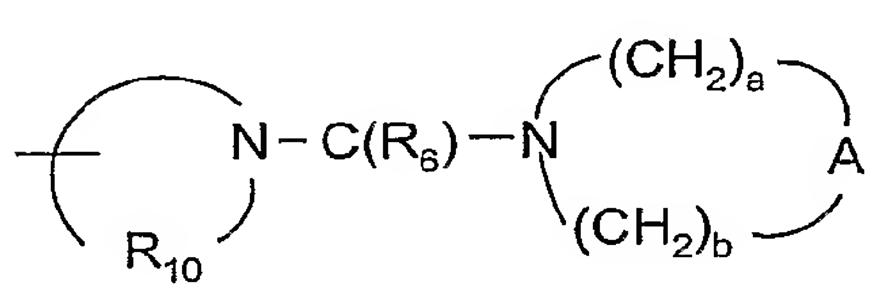
, and

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

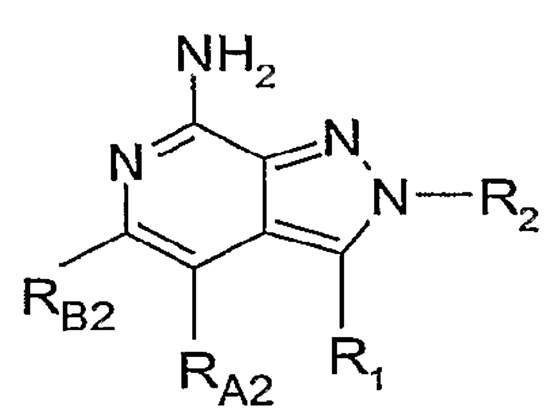
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides compounds of the formula (IX):



IX

wherein:

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5;

R_2 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

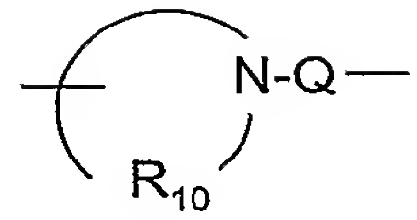
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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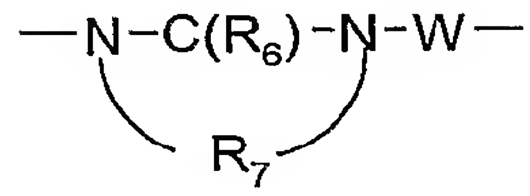

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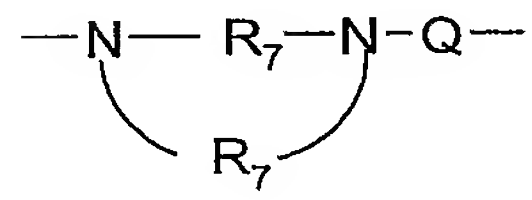

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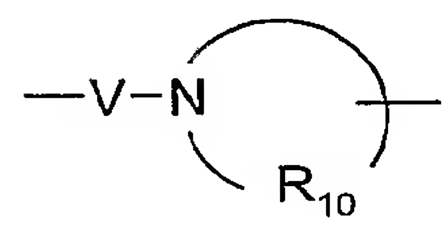

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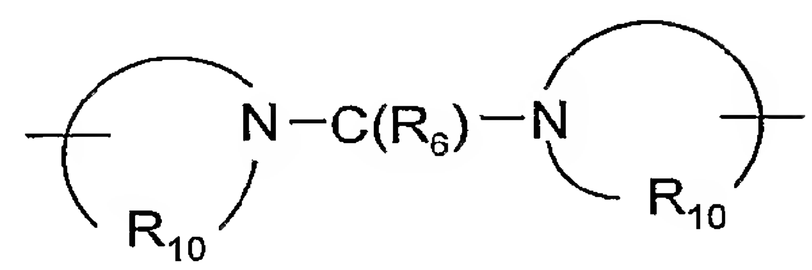
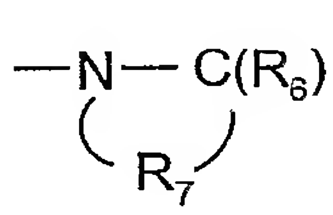
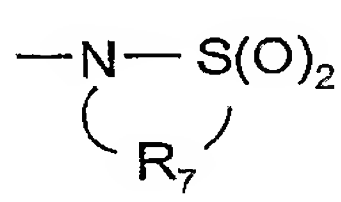
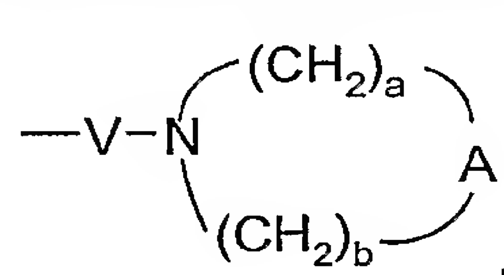
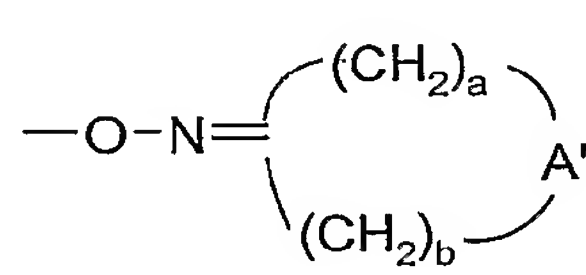
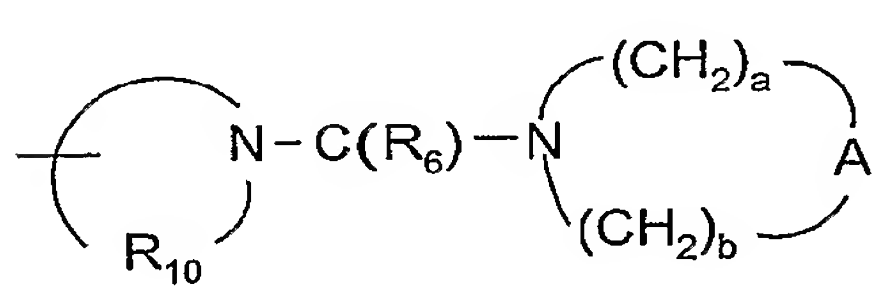


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

 ,  ,  ,  , and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

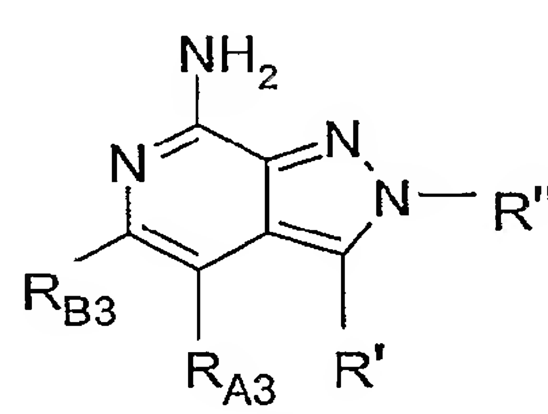
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

with the proviso that at least one of R_{A2}, R_{B2}, R_1, or R_2 is other than hydrogen;

or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides compounds of the formula (Ia):



Ia

wherein:

R_{A3} and R_{B3} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_{A3} and R_{B3} form a fused aryl ring or heteroaryl ring

containing one heteroatom or 5 to 7 membered saturated ring optionally containing one heteroatom wherein the heteroatom is selected from the group consisting of N and S and wherein the aryl, heteroaryl, or 5 to 7 membered saturated ring optionally containing one heteroatom is unsubstituted or substituted by one or more non-interfering substituents;

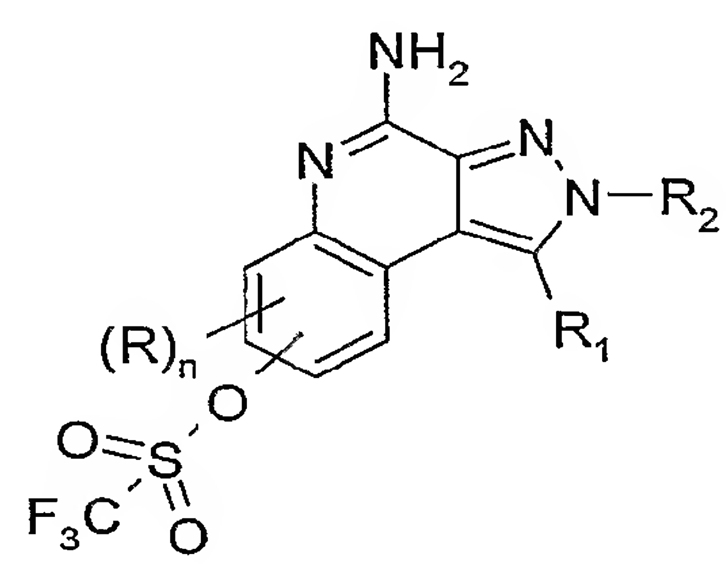
R' and R" are independently selected from the group consisting of hydrogen and non-interfering substitutents; and

R_9 is selected from the group consisting of hydrogen and alkyl;

with the proviso that at least one of R_{A3}, R_{B3}, R', or R" is other than hydrogen; and with the further proviso that when R_{A3} and R_{B3} form a benzene ring unsubstituted or substituted with chloro, and R' is hydrogen, then R" is other than phenyl or phenyl substituted with methyl, methoxy, chloro, or fluoro;

or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention provides compounds of the following formula (LXXX):



LXXX

wherein:

R is selected from the group consisting of:

halogen,

alkyl,

alkenyl,

trifluoromethyl, and

dialkylamino;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

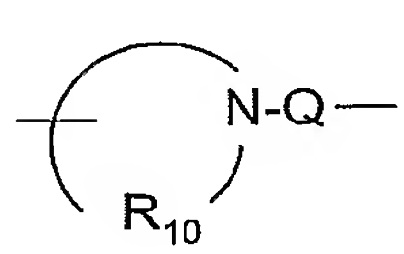
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

$-CH(-N(-O-R_8)-Q-R_4)-$,



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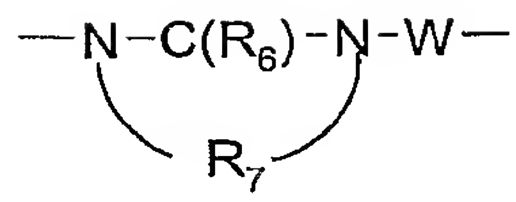
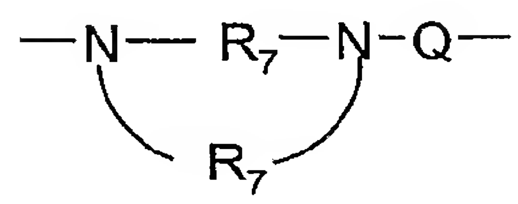
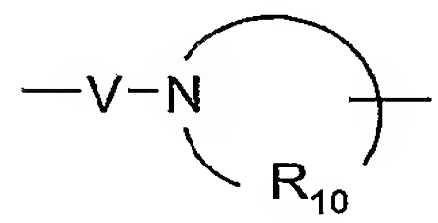
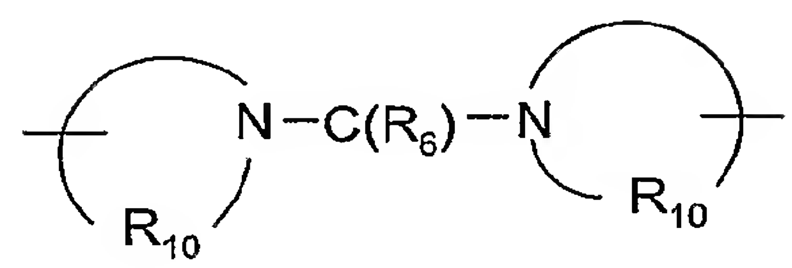
,

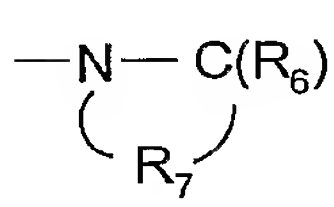
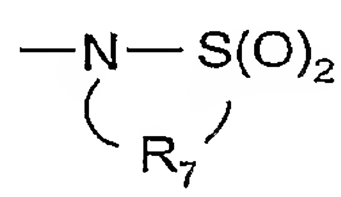
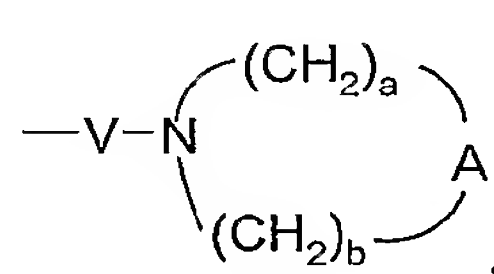
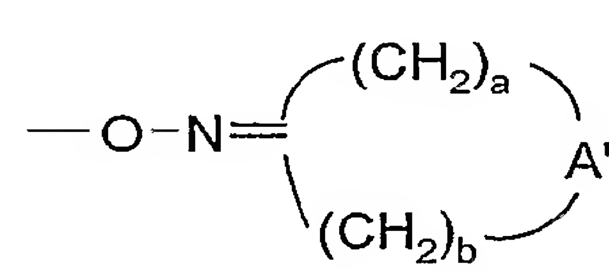
,

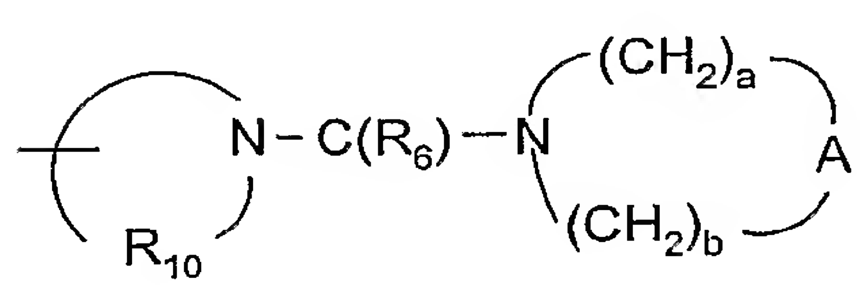
, and

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof. Compounds of Formula LXXX are useful, for example, as intermediates in the preparation of compounds of Formulas I, Ia, II, III, and VIII.

Herein, “non-interfering” means that the ability of the compound or salt, which contains a non-interfering substituent, to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. Illustrative non-interfering R' groups include those described herein for R_1. Illustrative non-interfering R" groups include those described herein for R_2. Illustrative non-interfering substituents (e.g., R''') for a substituted, fused aryl or heteroaryl ring, formed when R_A and R_B (in Formula I) or R_{A3} and R_{B3} (in Formula Ia) are taken together, include those described herein for R and R_3. Illustrative non-interfering substituents for a substituted, fused 5 to 7 membered saturated ring optionally containing one heteroatom, formed when R_A and R_B (in Formula I) or R_{A3} and R_{B3} (in Formula Ia) are taken together, include those described herein for R.

As used herein, the terms “alkyl”, “alkenyl”, “alkynyl” and the prefix “alk-” are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl

groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are use when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), homopiperazinyl (diazepanyl), 1,3-dioxolanyl,

aziridinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and the like. When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene," "heteroarylene," and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_8)-C(R_6)-N(R_8)-$ each R_8 group is independently selected. In another example, when an R_2 and an R_3 group both contain an R_4 group, each R_4 group is independently selected. In a further example, when more than one Y group is present (i.e., R_2 and R_3 both contain a Y group) and each Y group contains one or more R_8 groups, then each Y group is independently selected, and each R_8 group is independently selected.

The invention is inclusive of the compounds described herein and salts thereof, in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" or the term "compounds" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

In some embodiments, compounds of the invention (for example, compounds of Formulas Ia and I-IX, including embodiments thereof described herein) induce the biosynthesis of one or more cytokines, for example, IFN-α and/or TNF-α.

In some embodiments, compounds of the invention (for example, compounds of Formulas Ia and I-IX, including embodiments thereof described herein) inhibit the biosynthesis of one or more cytokines, for example, TNF-α.

For any of the compounds presented herein, each one of the following variables (e.g., R, R', R'', R''', R_1, R_2, R_3, n, m, A, X, Y, Z, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments, each of R, R', R'', and R''' is independently a non-interfering substituent. For certain embodiments, each R' and R'' is independently selected from the group consisting of hydrogen and non-interfering substituents.

In some embodiments of Formula I, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more non-interfering substituents; or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more substituents selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$.

In some embodiments of Formula I, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups; or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups; wherein each R is independently selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$.

In some embodiments of Formula I, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

In some embodiments of Formula I, R_A and R_B form a fused aryl or heteroaryl ring.

In some embodiments of Formula I, R_A and R_B form a fused 5 to 7 membered saturated ring.

In some embodiments of Formula II, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio and $-N(R_9)_2$; or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group; or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups; wherein R is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; and R_3 is selected from the group consisting of $-Z-R_4$, $-Z-X-R_4$, $-Z-X-Y-R_4$, $-Z-X-Y-X-Y-R_4$, and$-Z-X-R_5$.

In some embodiments of Formula II, R_{A1} and R_{B1} form a fused benzene ring which is unsubstituted.

In some embodiments of Formula II, R_{A1} and R_{B1} form a fused pyridine ring which is unsubstituted.

In some embodiments of Formula II, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted.

In some embodiments of Formula IX, R_{A2} and R_{B2} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. In certain of these embodiments, R_{A2} and R_{B2} are each independently alkyl. In certain of these embodiments, R_{A2} and R_{B2} are each methyl.

In some embodiments of Formula Ia, R_{A3} and R_{B3} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_{A3} and R_{B3} form a fused aryl ring or heteroaryl ring containing one heteroatom or a 5 to 7 membered saturated ring containing one heteroatom wherein the heteroatom is selected from the group consisting of N and S and wherein the aryl, heteroaryl, or 5 to 7 membered saturated ring is unsubstituted or substituted by one or more non-interfering substituents.

In some embodiments (e.g., of Formulas I through VIII), R is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$.

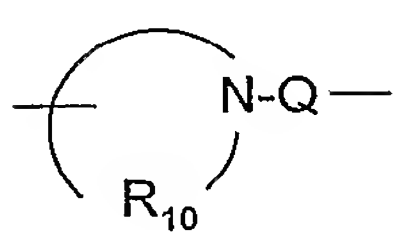
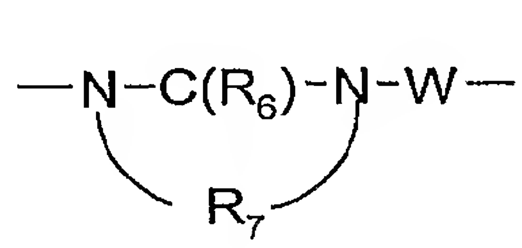
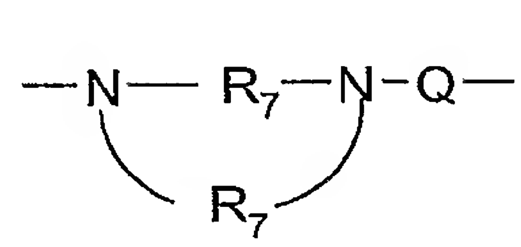
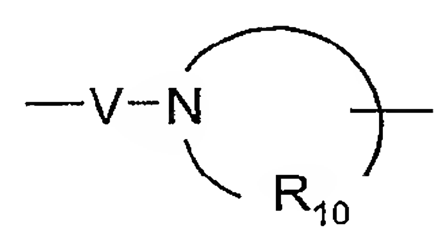
In some embodiments (e.g., of Formula III), R is selected from the group consisting of hydroxy and methoxy. In certain of these embodiments, m is 0. In certain of these embodiments, m is 0 and n is 1.

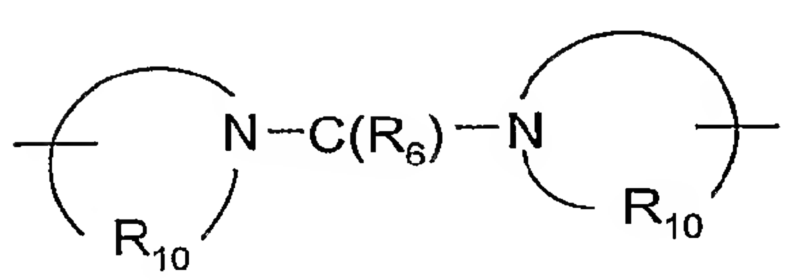
In some embodiments (e.g., of Formula LXXX), R is selected from the group consisting of halogen, alkyl, alkenyl, trifluoromethyl, and dialkylamino.

In some embodiments of Formulas I and Ia, R' is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, $-X-Y-X-Y-R_4$, and $-X-R_5$; wherein:

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, -O-C(O)-O-, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-O-N(R_8)-Q-$, $-O-N=C(R_4)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,

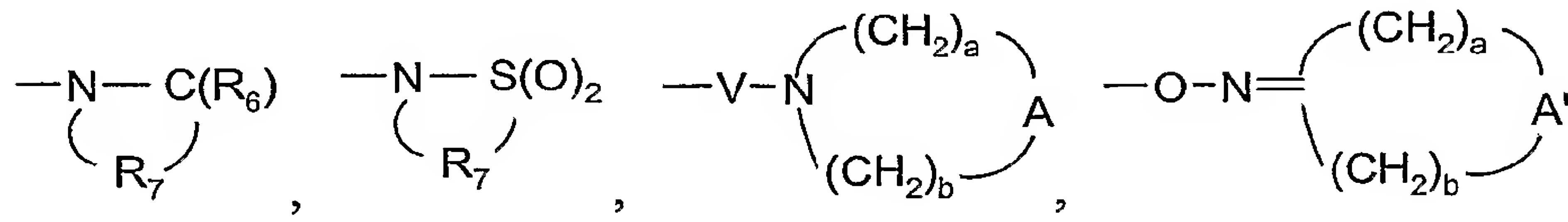
 ,  ,  ,  , and

 ;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,

(dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



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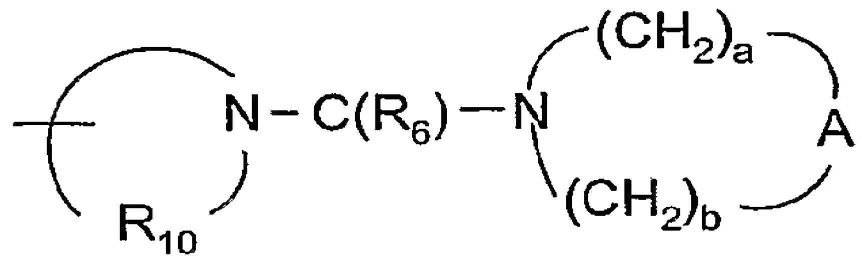


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, and –N(R_4)-;

A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH$_2$-;

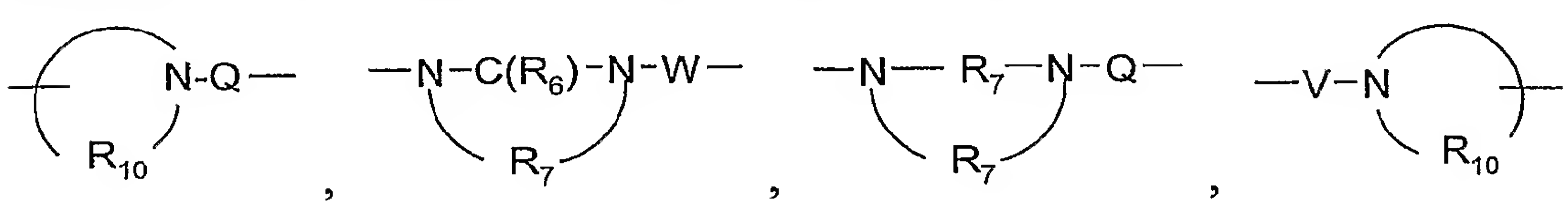
Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7.

In certain of these embodiments of Formulas I and Ia, Y is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,



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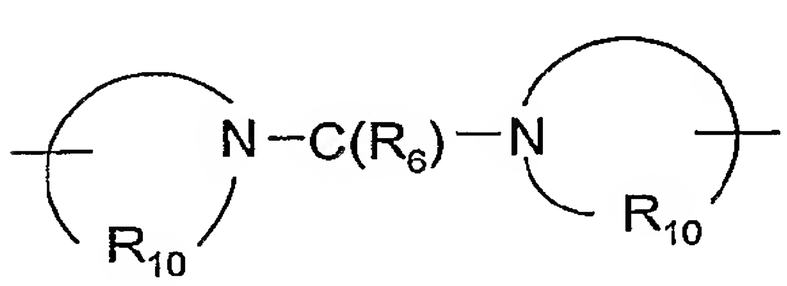
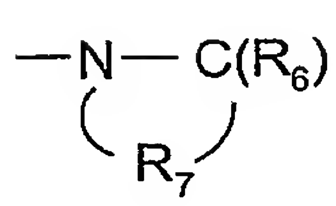
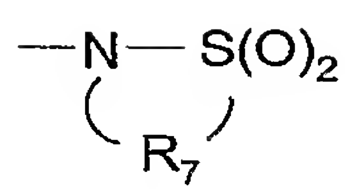
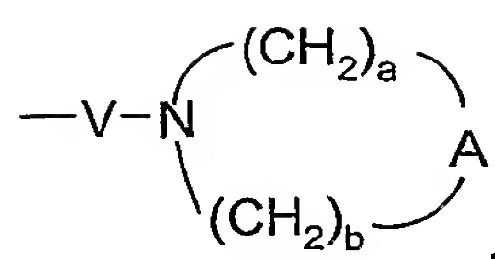
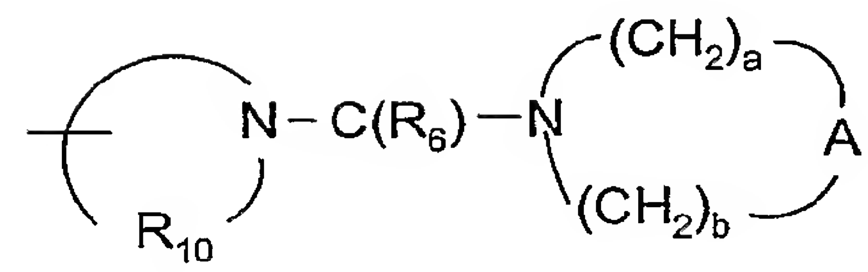
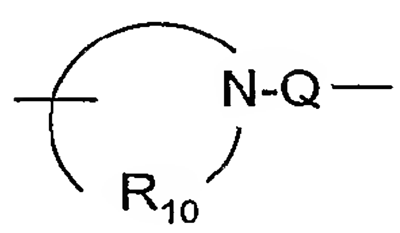
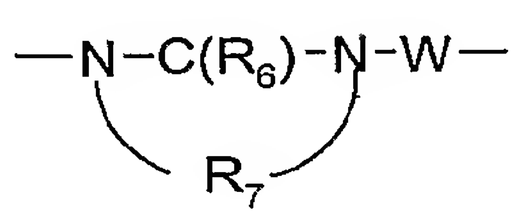
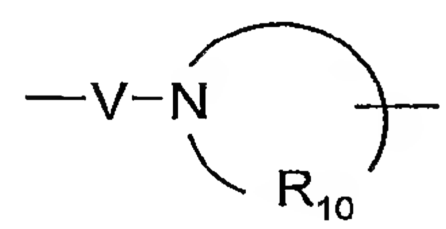
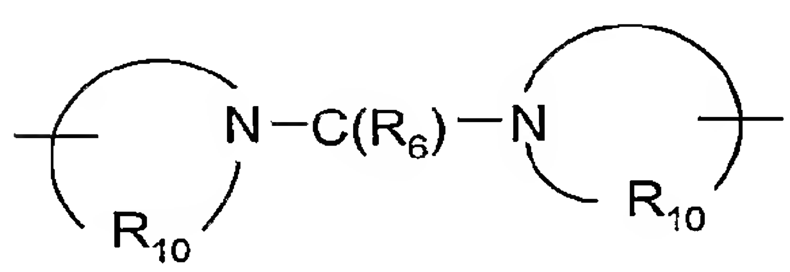


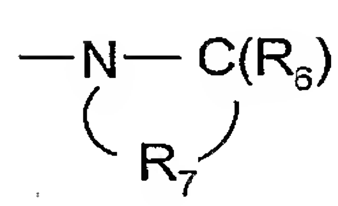
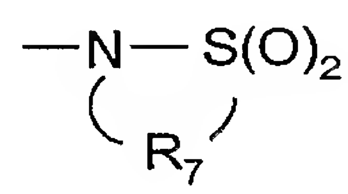
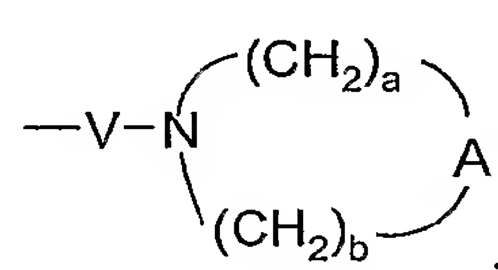
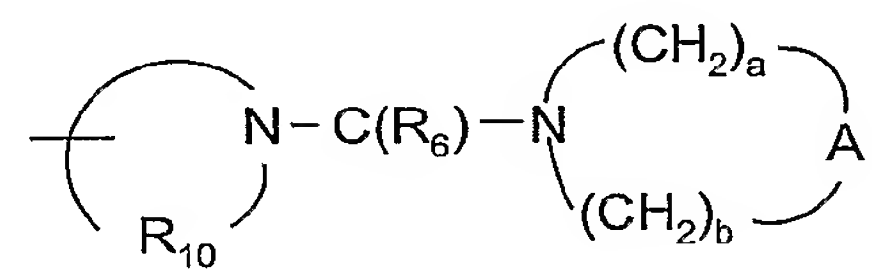
; R_5 is selected from the group consisting of

 ,  ,  , and  ;

and R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl. In certain of these embodiments, Y is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,

 ,  ,  , and

 ; R_5 is selected from the group consisting of

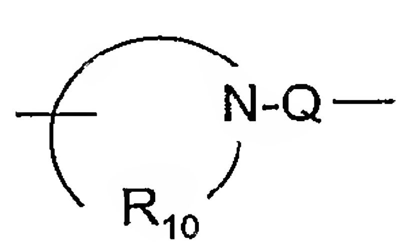
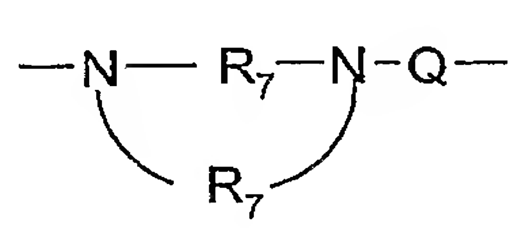
 ,  ,  , and  ;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl; and Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-.

In some embodiments of Formulas I and Ia, R' is selected from the group consisting of -R_4, -X-R_4, -X-Y-R_4, -X-Y-X^1-Y^1-R_4, and -X-R_5; wherein:

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group;

Y is selected from the group consisting of -O-, -S(O)$_2$-, -S(O)$_2$-N(R_8)-, -C(O)-, -C(O)-O-, -O-C(O)-, -N(R_8)-Q-, -C(O)-N(R_8)-,

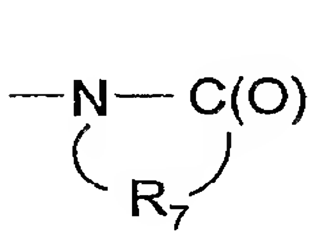
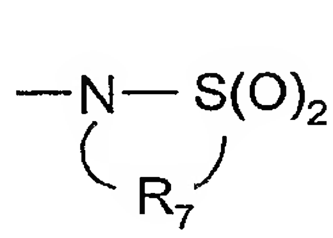
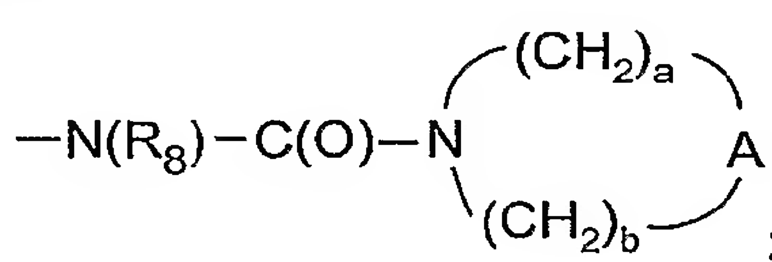
 , and  ;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of -S-, -C(O)-, -C(O)-O-, -C(O)-N(R_8)-, -S(O)$_2$-N(R_8)-, and -N(R_8)-C(O)-;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

 ,  , and  ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

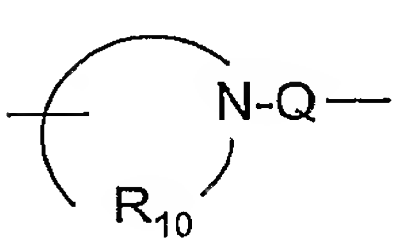
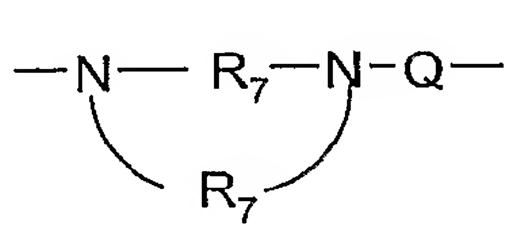
A is selected from the group consisting of -O-, -C(O)-, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

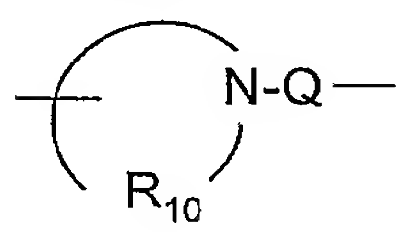
a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7.

In certain of these embodiments of Formulas I and Ia, X is alkylene that is optionally interrupted or terminated by heterocyclylene; Y is selected from the group consisting of $-S(O)_2-$, -C(O)-, -C(O)-O-, -O-C(O)-, $-N(R_8)-Q-$, $-C(O)-N(R_8)-$,

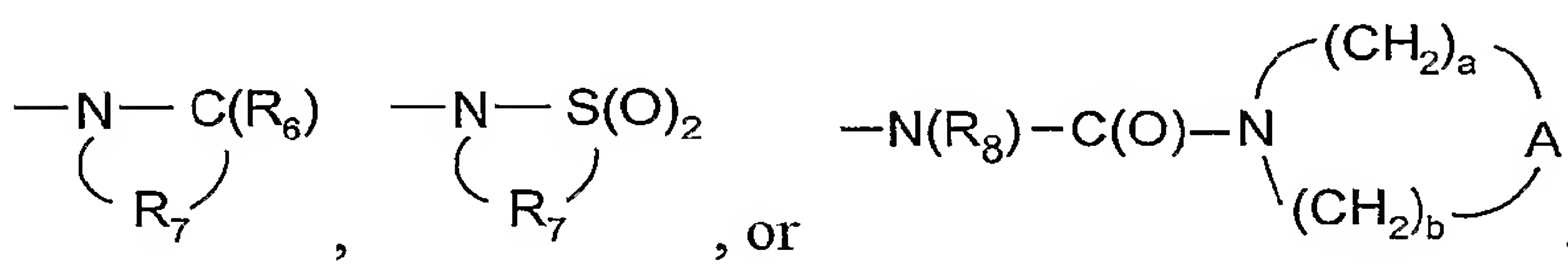
 , and  ; R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, and arylalkenylenyl, wherein the alkyl, aryl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of the

case of alkyl and heterocyclyl, oxo; and R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl.

In some embodiments of Formulas I and Ia, R' is selected from the group consisting of alkyl, arylalkylenyl, heterocyclylalkylenyl wherein heterocyclyl is unsubstituted or substituted with one or two oxo groups, aryloxyalkylenyl, hydroxyalkylenyl, aminoalkylenyl, haloalkylenyl, alkylsulfonylalkylenyl, -X-Y-R_4, and -X-R_5; wherein X is alkylene; Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-C(S)-N(R_8)-, -N(R_8)-S(O)$_2$-N(R_8)-, or



; R_4 is alkyl, aryl, or heteroaryl; and R_5 is



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In some embodiments of Formulas I and Ia, R' is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkynyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl, aryl-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl-O-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-4} alkyl-C(O)-O-C_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl, aryl-C(O)-NH-C_{1-4} alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-S(O)$_2$-C_{1-4} alkylenyl, amino-S(O)$_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one or two substituents selected from the group consisting of heteroaryl and oxo.

In some embodiments of Formulas I and Ia, R' is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, butyl, pent-4-ynyl, 2-

phenylethyl, 2-hydroxy-2-methylpropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-methanesulfonylethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 4-methanesulfonylaminobutyl, 2-methyl-2-[(methylsulfonyl)aminopropyl, 2-(2-propanesulfonylamino)ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-(isobutyrylamino)-2-methylpropyl, 2-methyl-2-(propionylamino)propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-(isobutyrylamino)ethyl, 2-{[(isopropylamino)carbonyl]amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

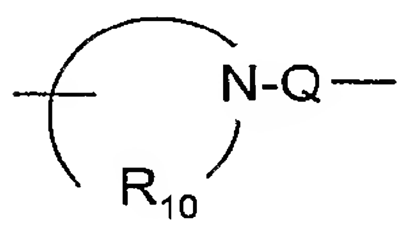
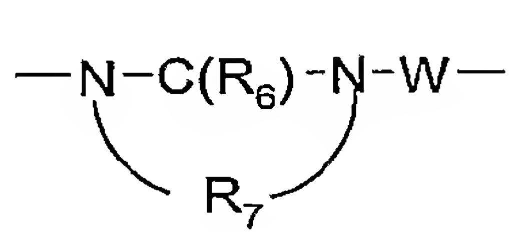
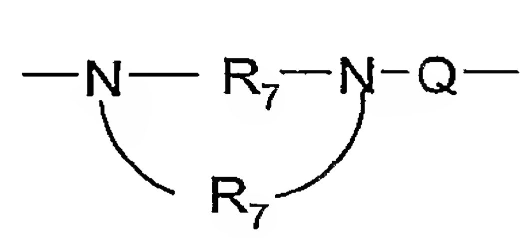
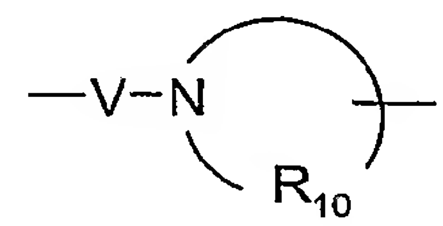
In some embodiments of Formulas I and Ia, R' is is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl.

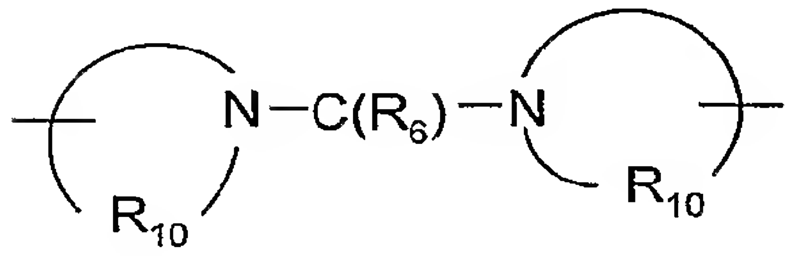
In some embodiments of Formulas I and Ia, R'' is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, and $-X-R_5$; wherein:

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

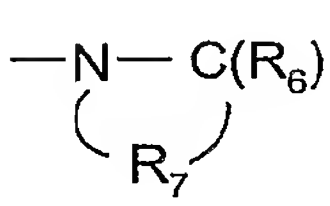
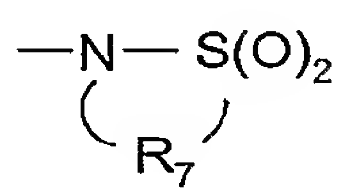
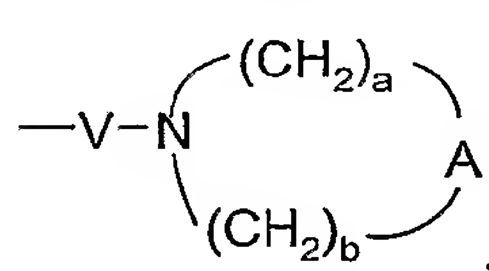
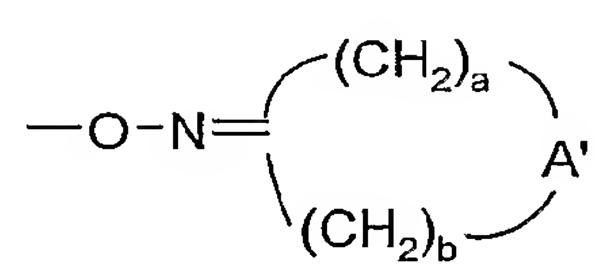
Y is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, -O-C(O)-O-, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-O-N(R_8)-Q-$, $-O-N=C(R_4)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,

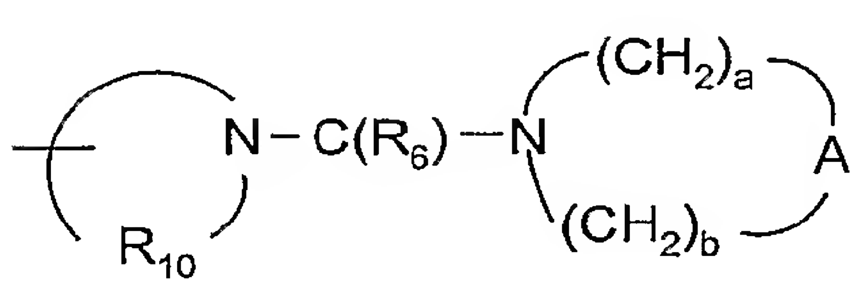
, , , , and

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, and –N(R_4)-;

A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

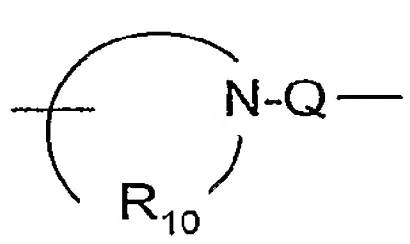
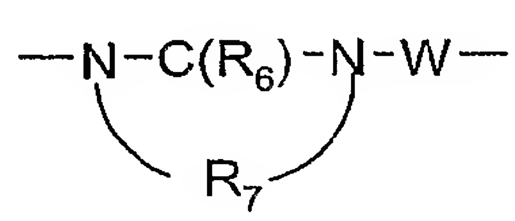
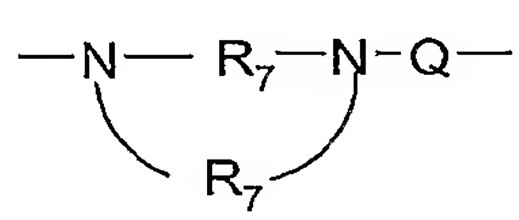
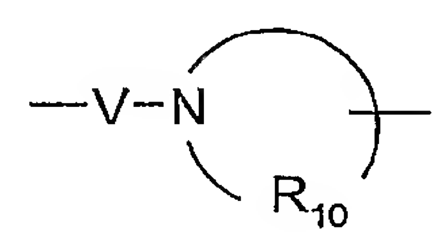
Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

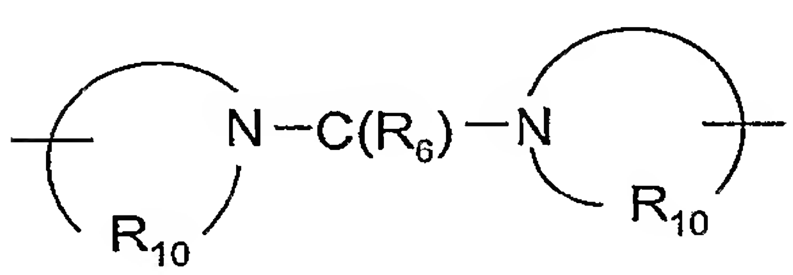
V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

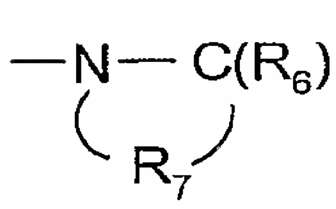
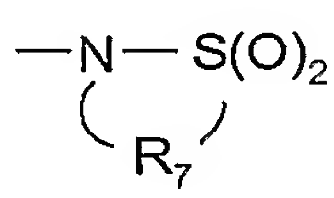
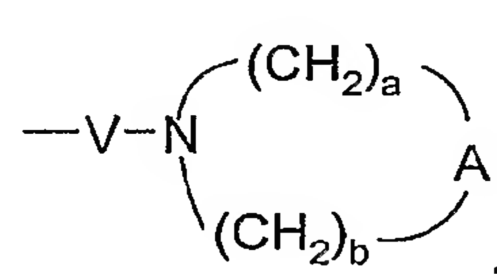
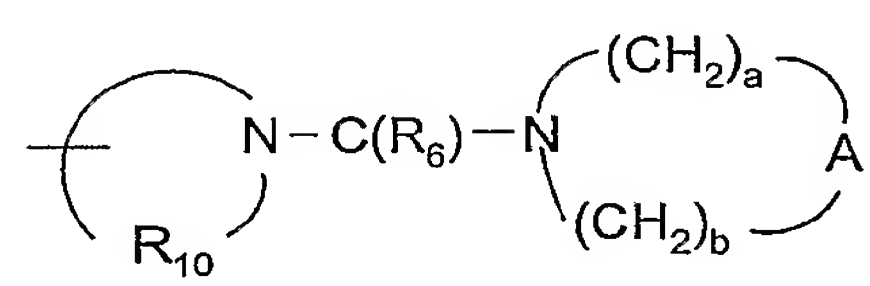
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

In certain of these embodiments of Formulas I and Ia, Y is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,

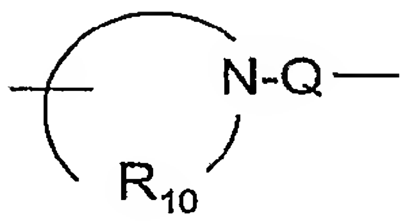
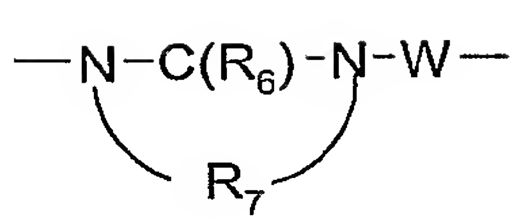
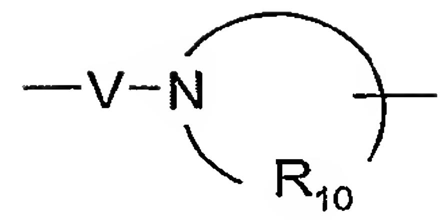
, , , , and

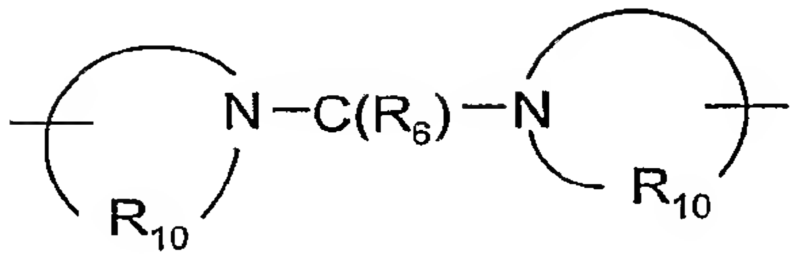
; and

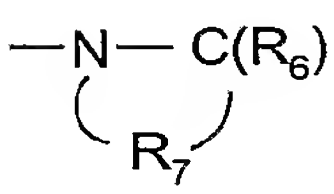
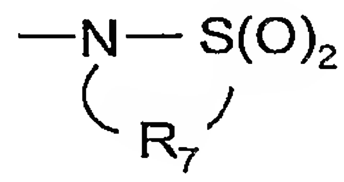
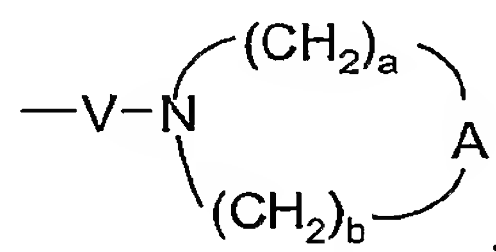
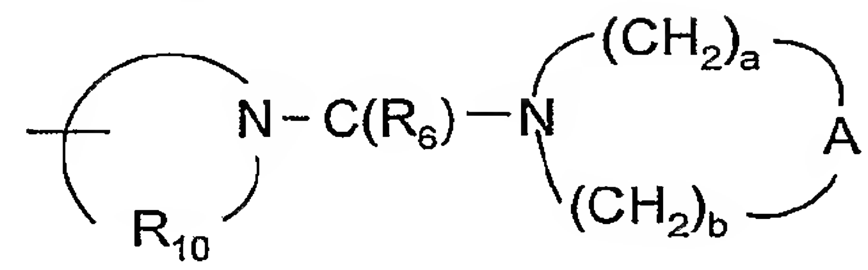
R_5 is selected from the group consisting of

, , , and ;

and R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl. In certain of these embodiments of Formulas I and Ia, Y is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,

, , , and

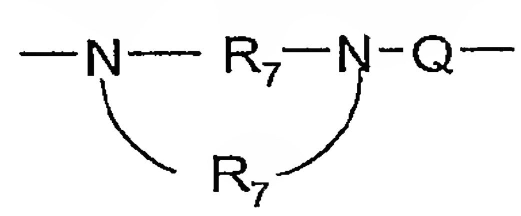
; R_5 is selected from the group consisting of

, , , and ;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl; and Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$.

In some embodiments of Formulas I and Ia, R'' is selected from the group consisting of $-R_4$, $-X-R_4$, and $-X-Y-R_4$; wherein:

X is alkylene that is optionally terminated by arylene or heterocyclylene;

Y is selected from the group consisting of $-S(O)_2-$, $-C(O)-$, $-C(O)-O-$, $-N(R_8)-Q-$, $-C(O)-N(R_8)-$, and ;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, heterocyclyl, and heteroaryl, wherein the alkyl, aryl, aryloxyalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, and in the case of heterocyclyl, oxo;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is in selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl; and

Q is selected from the group consisting of a bond, $-C(O)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-$, and $-S(O)_2-N(R_8)-$.

In some embodiments of Formulas I and Ia, R" is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl, and hydroxyalkylenyl. In certain embodiments, R" is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, and alkoxyalkylenyl. In certain embodiments, R" is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

In some embodiments of Formulas I and Ia, R" is selected from the group consisting of hydrogen, C_{1-5} alkyl, C_{1-4} alkoxyC_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, and arylC_{1-4} alkylenyl wherein aryl is unsubstituted or substituted by one or more substituents selected from the group consisting of chloro, fluoro, methoxy, methyl, cyano, and methoxycarbonyl. In certain embodiments, R" is selected from the group consisting of hydrogen, C_{1-5} alkyl, C_{1-4} alkoxyC_{1-4} alkylenyl, and arylC_{1-4} alkylenyl wherein aryl is unsubstituted or substituted by one or more substituents selected from the group consisting of chloro, fluoro, methoxy, methyl, cyano, and methoxycarbonyl. In certain embodiments, R" is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxyC_{1-4} alkylenyl.

In some embodiments of Formulas I and Ia, R" is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, and benzyl. In certain embodiments, R" is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, and benzyl. In certain embodiments, R" is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, and benzyl. In certain embodiments, R" is selected from the group consisting of methyl, ethyl, propyl, and butyl.

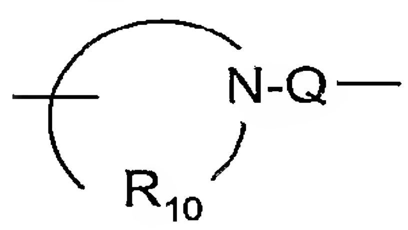
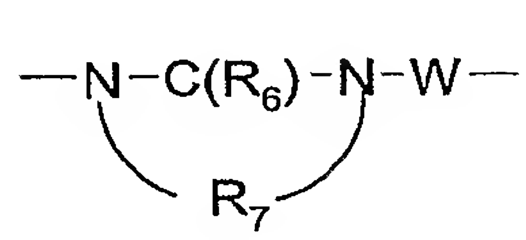
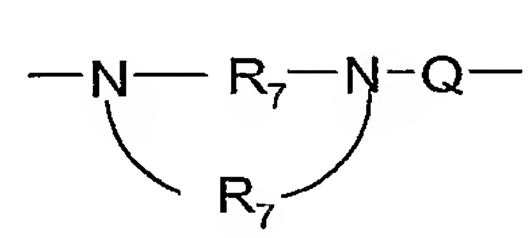
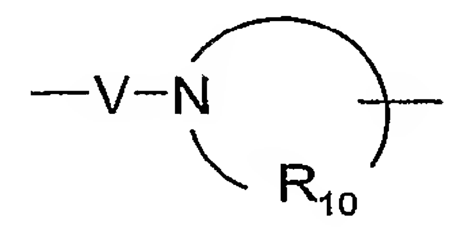
In some embodiments of Formula I, one or more R"' groups are present. In certain of these embodiments, R"' is one or more R groups, or one R group and one R_3 group, or one R_3 group.

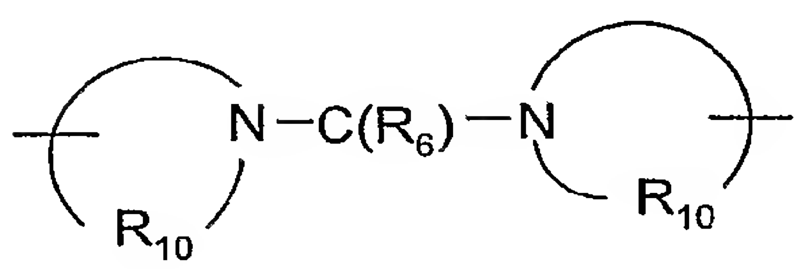
In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, $-X-Y-X-Y-R_4$, and $-X-R_5$; wherein:

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

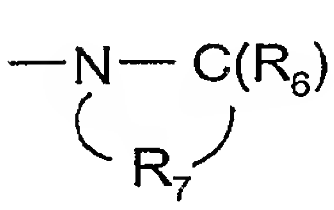
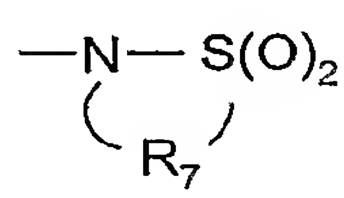
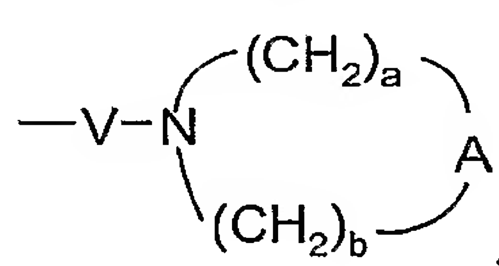
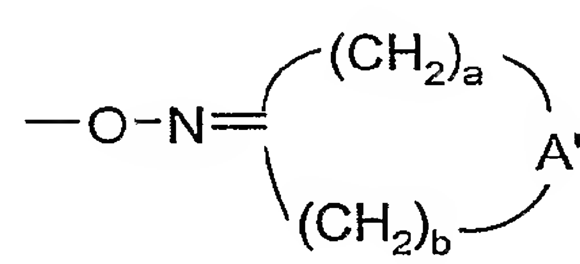
Y is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, -O-C(O)-O-, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-O-N(R_8)-Q-$, $-O-N=C(R_4)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,

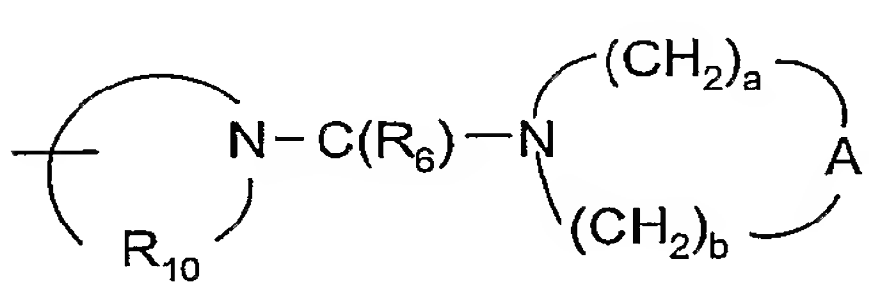
, , , , and

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, and –N(R_4)-;

A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

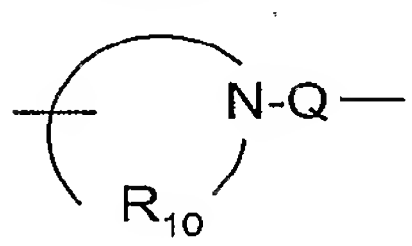
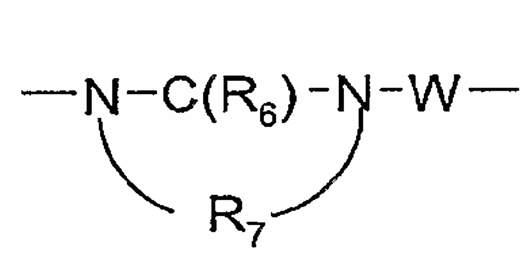
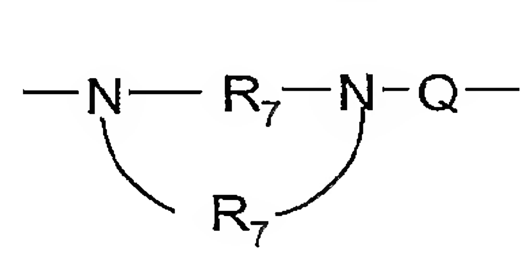
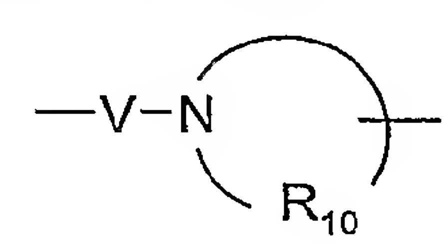
Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

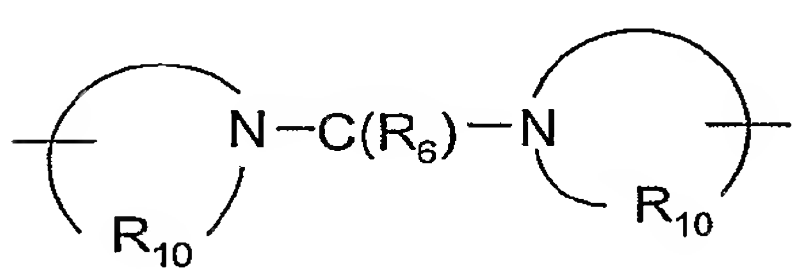
V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

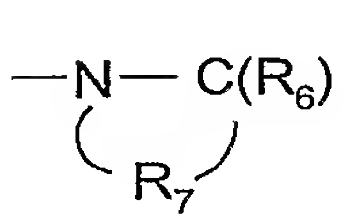
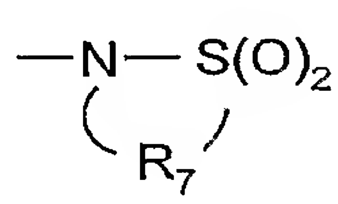
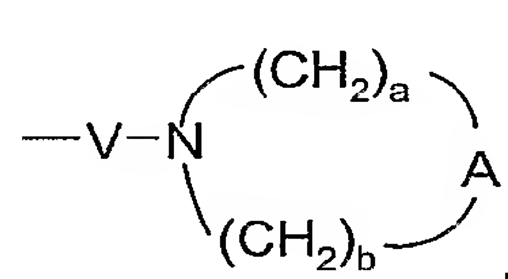
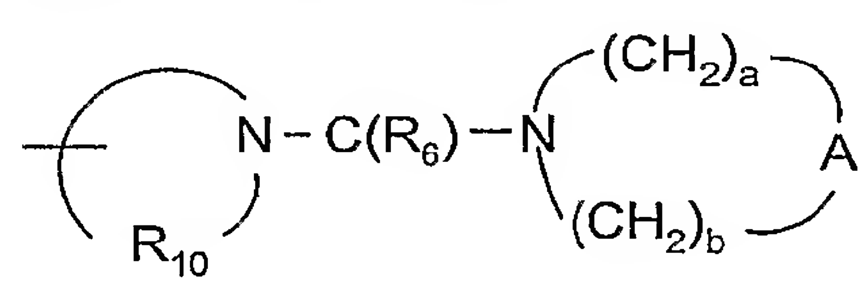
W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

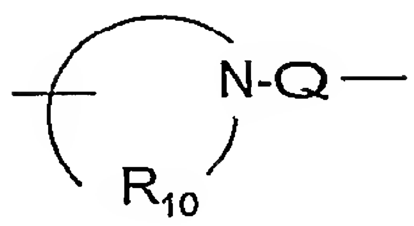
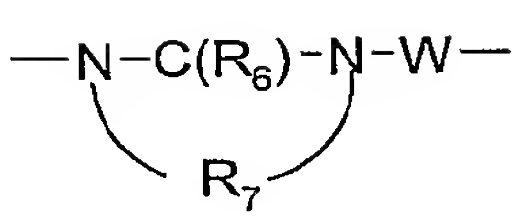
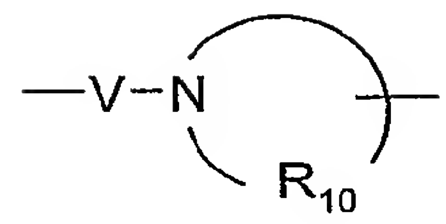
In certain of these embodiments (e.g., of Formulas II through IX and LXXX), Y is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,

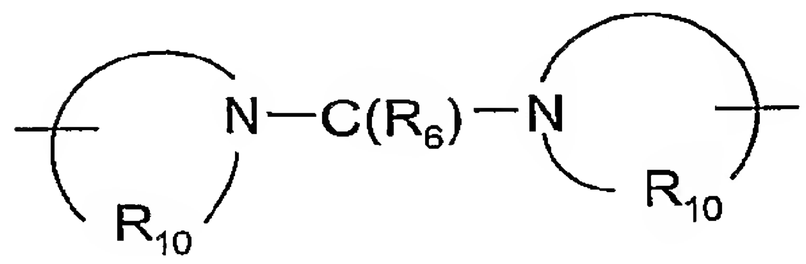
, , , , and

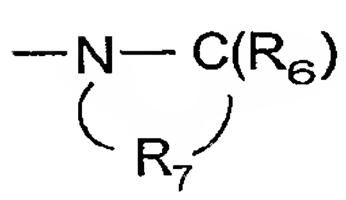
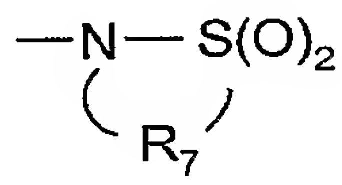
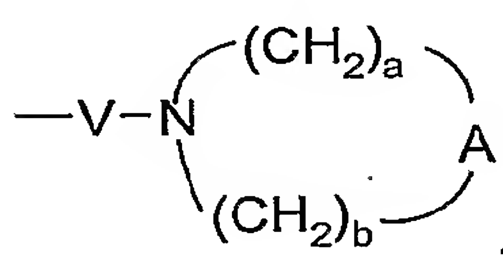
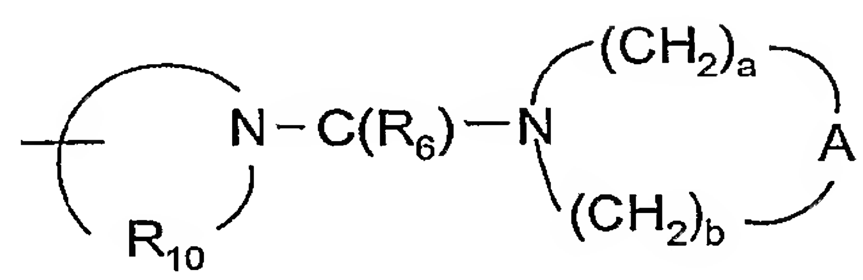
; R_5 is selected from the group consisting of

, , , and ;

and R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl. In certain of these embodiments, Y is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,

, , , and

; R_5 is selected from the group consisting of

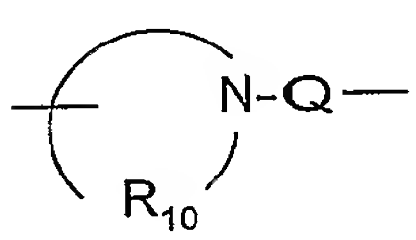
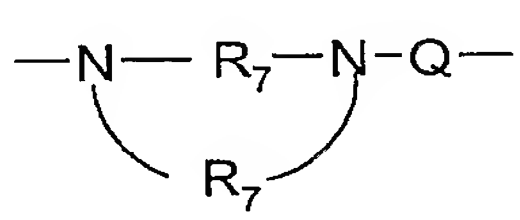
, , , and ;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl; and Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, $-X-Y-X^1-Y^1-R_4$, and $-X-R_5$; wherein:

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group;

Y is selected from the group consisting of -O-, $-S(O)_2-$, $-S(O)_2-N(R_8)-$, -C(O)-, -C(O)-O-, -O-C(O)-, $-N(R_8)-Q-$, $-C(O)-N(R_8)-$,

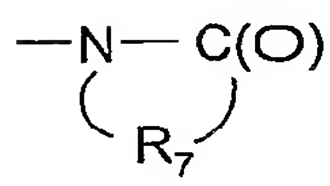
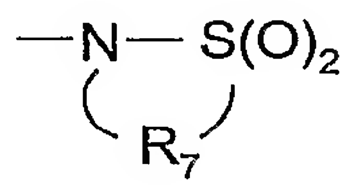
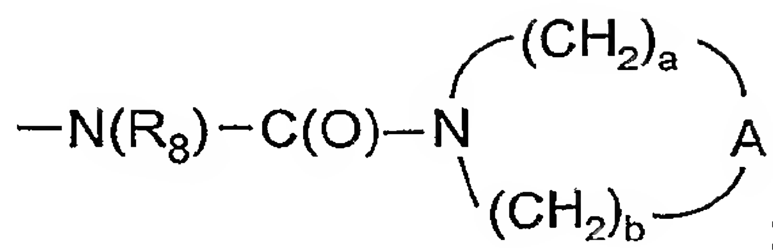
, and ;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of -S-, -C(O)-, -C(O)-O-, $-C(O)-N(R_8)-$, $-S(O)_2-N(R_8)-$, and $-N(R_8)-C(O)-$;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

R_5 is selected from the group consisting of

 ,  , and  ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

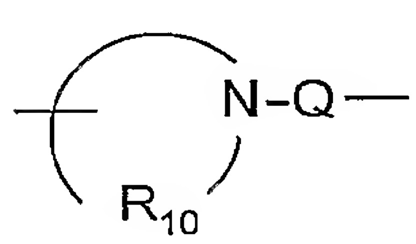
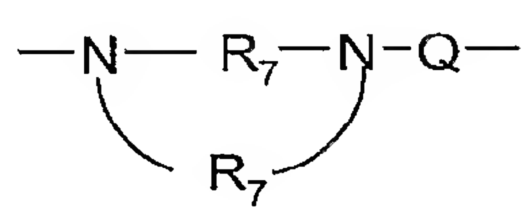
R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, and –N(R_4)-;

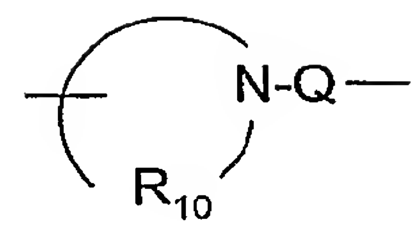
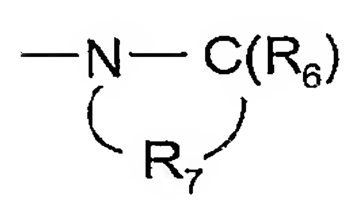
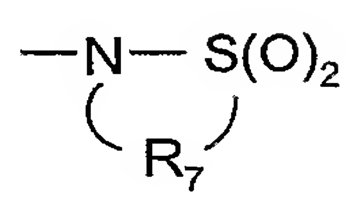
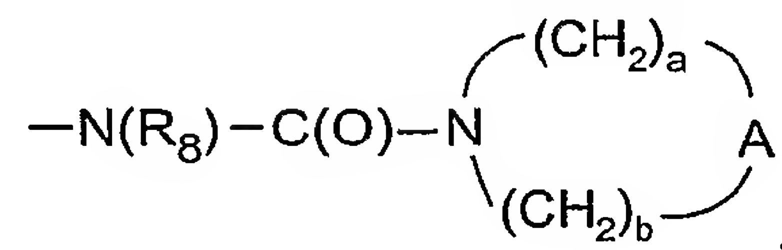
Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

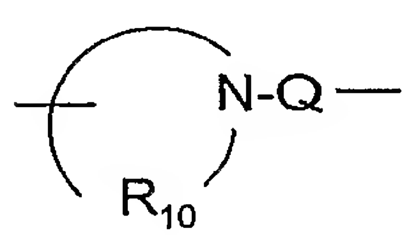
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.
In certain of these embodiments, X is alkylene that is optionally interrupted or terminated by heterocyclylene; Y is selected from the group consisting of -S(O)$_2$-, -C(O)-, -C(O)-O-, -O-C(O)-, -N(R_8)-Q-, -C(O)-N(R_8)-,

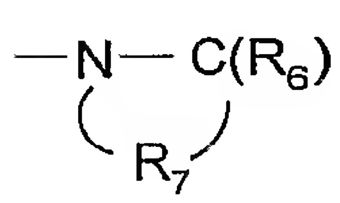
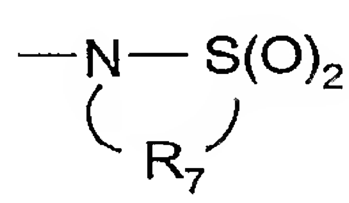
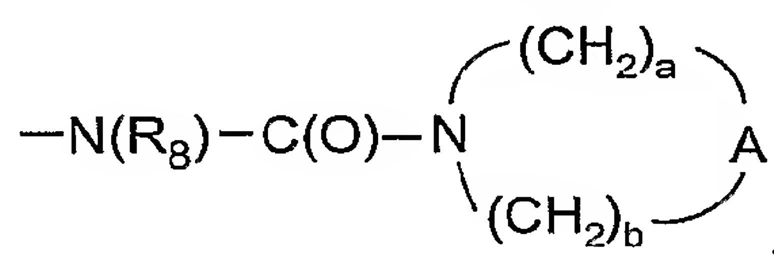
 , and  ; R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, and arylalkenylenyl, wherein the alkyl, aryl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo; and R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of alkyl, arylalkylenyl, heterocyclylalkylenyl wherein heterocyclyl is unsubstituted or substituted with one or two oxo groups, aryloxyalkylenyl, hydroxyalkylenyl, aminoalkylenyl, haloalkylenyl, alkylsulfonylalkylenyl, -X-Y-R_4, and -X-R_5; wherein X is alkylene; Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-,

$-N(R_8)-C(S)-N(R_8)-$, $-N(R_8)-S(O)_2-N(R_8)-$, or  ; R_4 is alkyl, aryl, or heteroaryl; and R_5 is  ,  , or  .

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, $-X-Y-R_4$, and $-X-R_5$; wherein X is alkylene; Y is $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-C(O)-N(R_8)-$, or

 ; R_4 is alkyl, aryl, or heteroaryl; and R_5 is

 ,  , or  .

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is $-R_4$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is $-X-R_4$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is $-X-Y-R_4$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is $-X-Y-X-Y-R_5$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is $-X-Y-X^1-Y^1-R_4$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is $-X-R_5$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkynyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-$S(O)_2$-C_{1-4} alkylenyl, aryl-$S(O)_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-$S(O)_2$-C_{1-4} alkylenyl-O-C_{1-4} alkylenyl, C_{1-4} alkyl-$S(O)_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-4} alkyl-C(O)-O-C_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl, aryl-C(O)-NH-C_{1-4} alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-$S(O)_2$-NH-C_{1-4} alkylenyl, aryl-$S(O)_2$-NH-C_{1-4} alkylenyl,

aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino–C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino–S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-S(O)$_2$-C_{1-4} alkylenyl, amino-S(O)$_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one or two substituents selected from the group consisting of heteroaryl and oxo.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of C_{1-5} alkyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl, aryl-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino–S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino–C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one or two substituents selected from the group consisting of heteroaryl and oxo.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of C_{1-4} alkyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl, aryl-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, and di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted with one or two oxo groups.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl,

butyl, pent-4-ynyl, 2-phenylethyl, 2-hydroxy-2-methylpropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-methanesulfonylethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 4-methanesulfonylaminobutyl, 2-methyl-2-[(methylsulfonyl)aminopropyl, 2-(2-propanesulfonylamino)ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-(isobutyrylamino)-2-methylpropyl, 2-methyl-2-(propionylamino)propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-(isobutyrylamino)ethyl, 2-{[(isopropylamino)carbonyl]amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

In some embodiments (e.g., of Formula VIII), R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, butyl, pent-4-ynyl, 2-cyclohexylethyl, 2-hydroxy-2-methylpropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-methanesulfonylethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 4-methanesulfonylaminobutyl, 2-methyl-2-[(methylsulfonyl)aminopropyl, 2-(2-propanesulfonylamino)ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl,

2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-(isobutyrylamino)-2-methylpropyl, 2-methyl-2-(propionylamino)propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-(isobutyrylamino)ethyl, 2-{[(isopropylamino)carbonyl]amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of methyl, ethyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-phenylethyl, 2-hydroxy-2-methylpropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 2-methanesulfonylethyl, 2-(propylsulfonyl)ethyl, 4-methanesulfonylaminobutyl, 2-methyl-2-[(methylsulfonyl)aminopropyl, 2-(2-propanesulfonylamino)ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-(isobutyrylamino)-2-methylpropyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-(isobutyrylamino)ethyl, 2-{[(isopropylamino)carbonyl]amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-

[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of methyl, 2-cyclohexylethyl, 2,2-dimethylpropyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 2-(benzoylamino)ethyl, 4-methanesulfonylaminobutyl, and 2-methylpropyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2-methanesulfonylethyl, and 4-methanesulfonylaminobutyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of 2-methylpropyl, 2,2-dimethylpropyl, ethyl, and 4-[(morpholin-4-ylcarbonyl)amino]butyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of 2-methylpropyl, 2,2-dimethylpropyl, and ethyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of methyl and 2-methylpropyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is 2-methylpropyl.

In some embodiments, R_1 is C_{1-4} alkyl. In certain embodiments, R_1 is straight chain C_{1-4} alkyl. In certain embodiments, R_1 is branched C_{1-4} alkyl.

In some embodiments, R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, and butyl.

In some embodiments, R_1 is selected from the group consisting of pent-4-ynyl and 2-phenylethyl. In certain embodiments, R_1 is 2-phenylethyl.

In some embodiments, R_1 is selected from the group consisting of 2-hydroxy-2-methylpropyl and 2-amino-2-methylpropyl. In certain embodiments, R_1 is 2-hydroxy-2-methylpropyl. In certain embodiments, R_1 is 2-amino-2-methylpropyl.

In some embodiments, R_1 is selected from the group consisting of 4-hydroxybutyl, 2-aminoethyl, 4-aminobutyl, 4-chlorobutyl, and 4-acetoxybutyl.

In some embodiments, R_1 is C_{1-4} alkyl-$S(O)_2$-C_{1-4} alkylenyl.

In some embodiments, R_1 is phenyl-$S(O)_2$-C_{1-4} alkylenyl.

In some embodiments, R_1 is selected from the group consisting of 2-methanesulfonylethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, and 3-(phenylsulfonyl)propyl.

In some embodiments, R_1 is C_{1-4} alkyl-$S(O)_2$-C_{1-4} alkyleneoxyC_{1-4} alkylenyl.

In some embodiments, R_1 is 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl.

In some embodiments, R_1 is C_{1-4} alkyl-$S(O)_2$-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is aryl-$S(O)_2$-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is diC_{1-4} alkyl-N-$S(O)_2$-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is selected from the group consisting of 4-methanesulfonylaminobutyl, 2-(benzenesulfonylamino)ethyl, 2-(2-propanesulfonylamino)ethyl, and 2-(dimethylaminosulfonylamino)ethyl. In certain embodiments, R_1 is 4-methanesulfonylaminobutyl.

In some embodiments, R_1 is C_{1-4} alkyl-C(O)-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is aryl-C(O)-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is heteroaryl-C(O)-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is selected from the group consisting of 2-(benzoylamino)ethyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, and 2-(isobutyrylamino)ethyl.

In some embodiments, R_1 is C_{1-6} alkyl-NH-C(O)-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is $N(C_{1-4}$ alkyl$)_2$-C(O)-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is aryl-NH-C(O)-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is heteroaryl-NH-C(R_6)-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is heterocyclyl-C(O)-NH-C_{1-4} alkylenyl.

In some embodiments, R_1 is selected from the group consisting of 4-[(morpholin-4-ylcarbonyl)amino]butyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(pyridin-3-ylamino)carbonyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

In some embodiments, R_1 is 2-methyl-2-[(methylsulfonyl)aminopropyl.

In some embodiments, R_1 is selected from the group consisting of 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-(isobutyrylamino)-2-methylpropyl, 2-methyl-2-(propionylamino)propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, and 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl.

In some embodiments, R_1 is 2-{[(isopropylamino)carbonyl]amino]-2-methylpropyl.

In some embodiments, R_1 is selected from the group consisting of 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, and 4-[(dimethylamino)sulfonyl]butyl.

In some embodiments, R_1 is heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl.

In some embodiments, R_1 is selected from the group consisting of 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, and 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl.

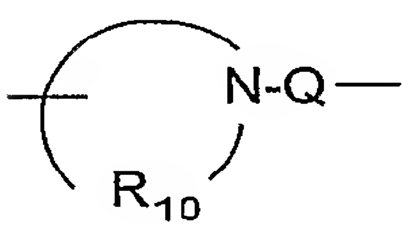
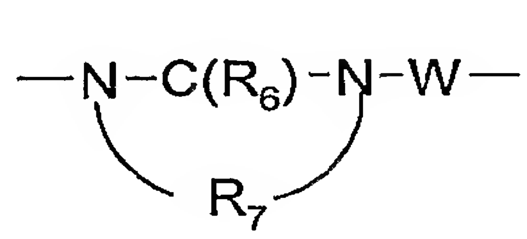
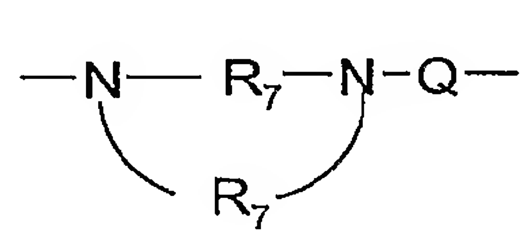
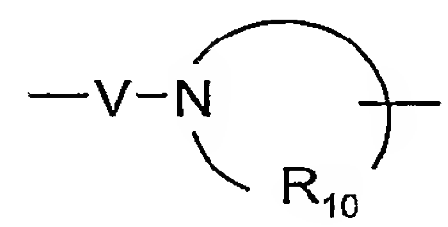
In some embodiments, R_1 is 4-(4-pyridin-2-ylpiperazin-1-yl)butyl.

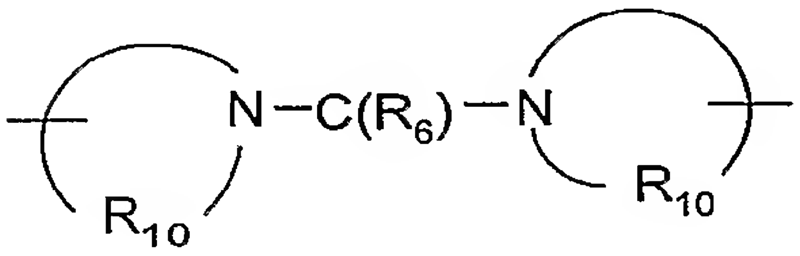
Each of the embodiments for R_1 described above can be combined with one or more embodiments for R_2 described below. Each of the resulting combinations is an embodiment.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is selected from the group consisting of $-R_4$, $-X-R_4$, $-X-Y-R_4$, and $-X-R_5$; wherein:

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

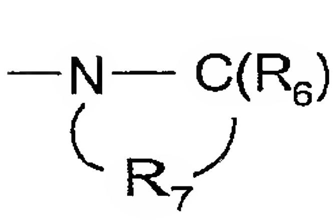
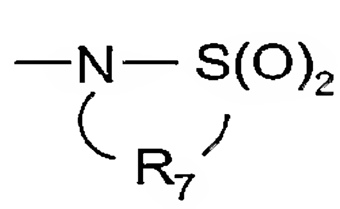
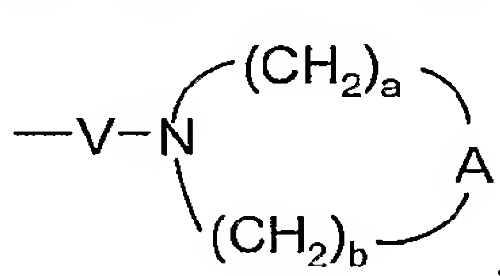
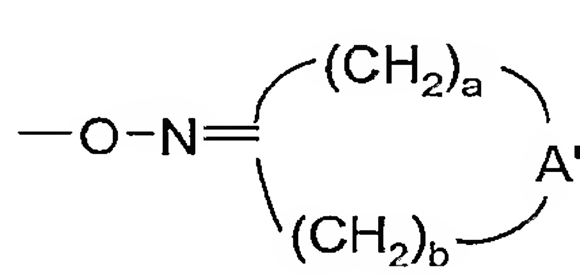
Y is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, -O-C(O)-O-, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-O-N(R_8)-Q-$, $-O-N=C(R_4)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,

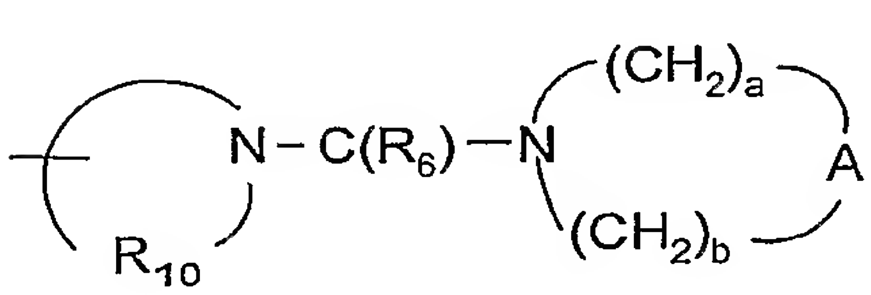
 ,  ,  ,  , and

 ;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

 ,  ,  ,  , and

 ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

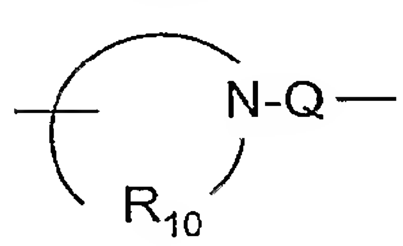
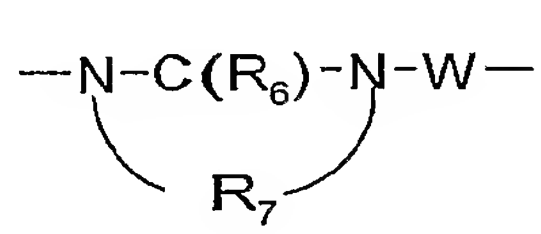
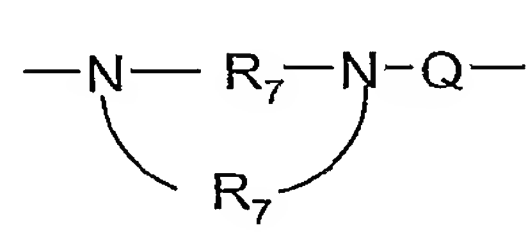
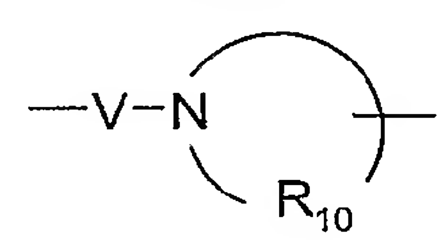
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

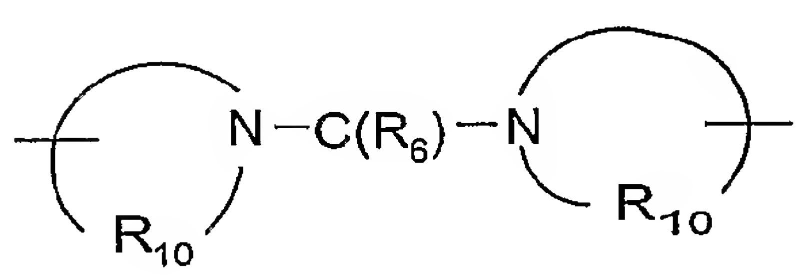
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

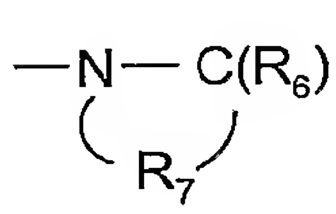
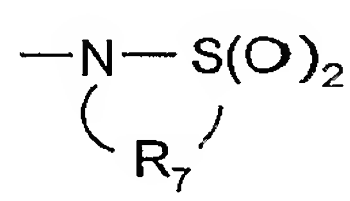
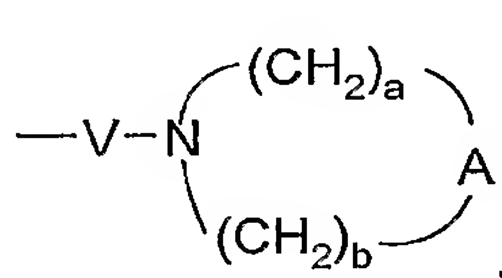
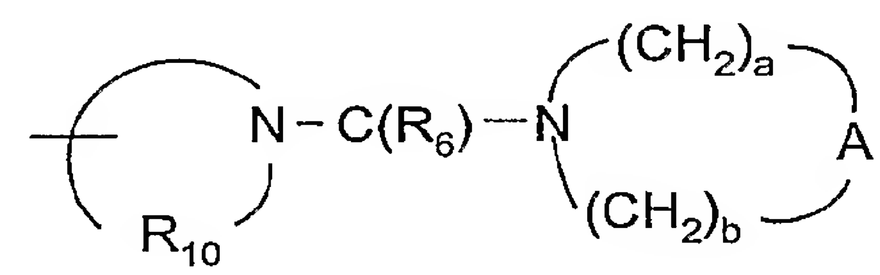
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

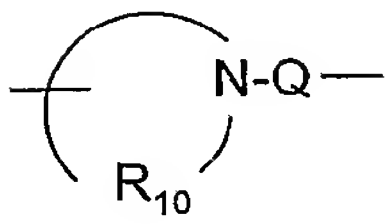
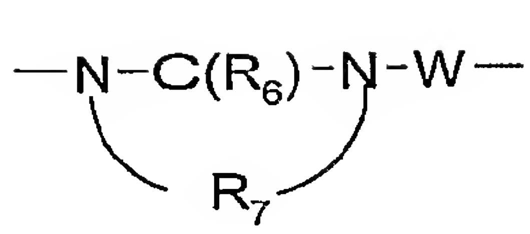
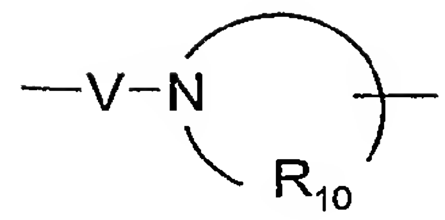
In certain of these embodiments (e.g., of Formulas II through IX and LXXX), Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, -O-C(O)-O-, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,

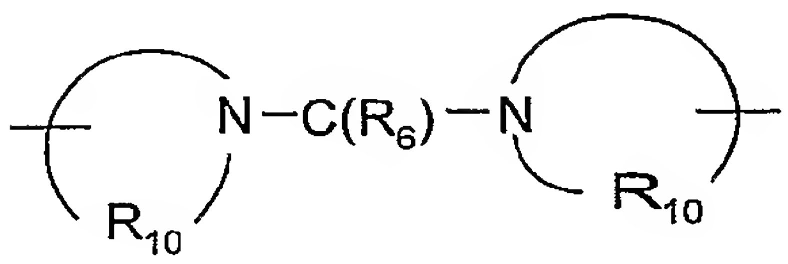
,
,
,
, and

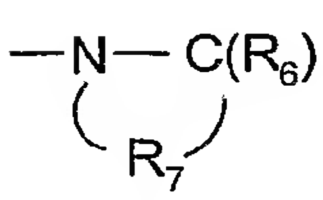
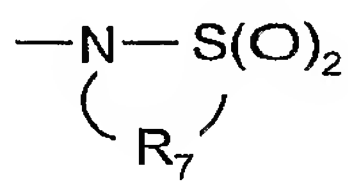
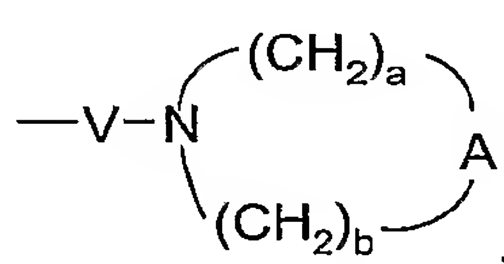
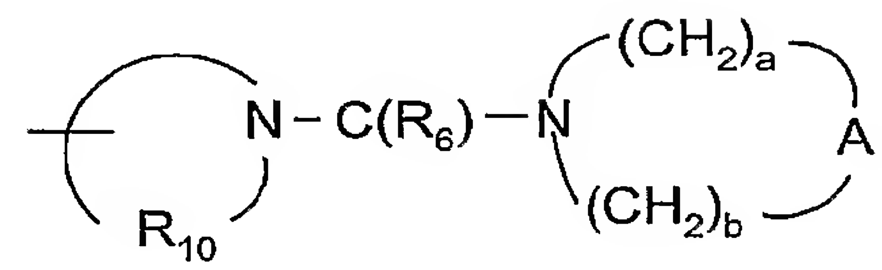
; R_5 is selected from the group consisting of

,
,
, and
;

and R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl. In certain of these embodiments (e.g., of Formulas II through IX and LXXX), Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, -O-C(O)-O-, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,

, , , and

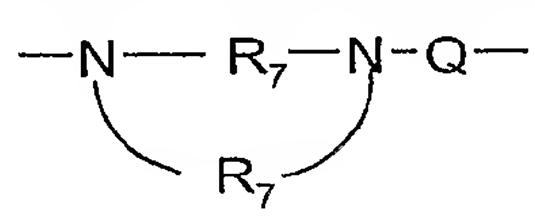
; R_5 is selected from the group consisting of

, , , and ;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl; and Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is selected from the group consisting of $-R_4$, $-X-R_4$, and $-X-Y-R_4$; wherein:

X is alkylene that is optionally terminated by arylene or heterocyclylene;

Y is selected from the group consisting of $-S(O)_2-$, $-C(O)-$, $-C(O)-O-$, $-N(R_8)-Q-$, $-C(O)-N(R_8)-$, and ;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, heterocyclyl, and heteroaryl, wherein the alkyl, aryl, aryloxyalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, and in the case of heterocyclyl, oxo;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is in selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl; and

Q is selected from the group consisting of a bond, $-C(O)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-$, and $-S(O)_2-N(R_8)-$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is $-R_4$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is $-X-R_4$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is $-X-Y-R_4$.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl, and hydroxyalkylenyl. In certain embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, and alkoxyalkylenyl. In certain embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is selected from the group consisting of hydrogen, C_{1-5} alkyl, C_{1-4} alkoxyC_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, and arylC_{1-4} alkylenyl wherein aryl is unsubstituted or substituted by one or more substituents selected from the group consisting of chloro, fluoro, methoxy, methyl, cyano, and methoxycarbonyl.

In some embodiments, R_2 is selected from the group consisting of hydrogen, C_{1-5} alkyl, C_{1-4} alkoxyC_{1-4} alkylenyl, and arylC_{1-4} alkylenyl wherein aryl is unsubstituted or substituted by one or more substituents selected from the group consisting of chloro, fluoro, methoxy, methyl, cyano, and methoxycarbonyl.

In some embodiments, R_2 is selected from the group consisting of hydrogen, C_{1-4} alkyl, and C_{1-4} alkoxyC_{1-4} alkylenyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, and benzyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, and benzyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, and benzyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is selected from the group consisting of methyl, ethyl, propyl, butyl, and benzyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is selected from the group consisting of methyl, ethyl, propyl, and butyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_2 is methyl.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl; and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, and benzyl. In certain of these embodiments, m and n are 0.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl; and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, and benzyl. In certain of these embodiments, m and n are 0.

In some embodiments (e.g., of Formulas II through IX and LXXX), R_1 is selected from the group consisting of 2-methylpropyl, 2,2-dimethylpropyl, ethyl, and 4-[(morpholin-4-ylcarbonyl)amino]butyl; and R_2 is selected from the group consisting of methyl, ethyl, propyl, butyl, and benzyl. In certain of these embodiments m and n are 0. In certain of these embodiments, R_1 is selected from the group consisting of 2-methylpropyl, 2,2-dimethylpropyl, and ethyl.

In some embodiments (e.g., of Formulas III through VII), R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2-methanesulfonylethyl, and 4-methanesulfonylaminobutyl; and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, and benzyl. In certain of these embodiments, m and n are 0.

In some embodiments (e.g., of Formulas III through VII), R_1 is 2-methylpropyl; and R_2 is selected from the group consisting of methyl, ethyl, propyl, and butyl. In certain of these embodiments, m and n are 0.

In some embodiments of Formula VIII, R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-cyclohexylethyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl; and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, and 2-hydroxyethyl. In certain of these embodiments, n is 0.

In some embodiments of Formula VIII, R_1 is selected from the group consisting of methyl, 2-cyclohexylethyl, 2,2-dimethylpropyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 2-(benzoylamino)ethyl, 4-methanesulfonylaminobutyl, and 2-methylpropyl; and R_2 is selected from the group consisting of methyl, ethyl, propyl, and butyl. In certain of these embodiments, n is 0.

In some embodiments of Formula VIII, R_1 is selected from the group consisting of methyl and 2-methylpropyl; R_2 is methyl. In certain of these embodiments, n is 0.

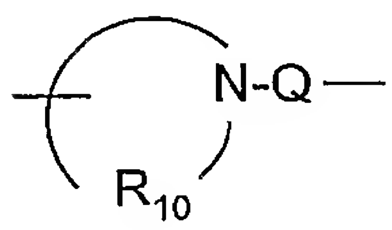
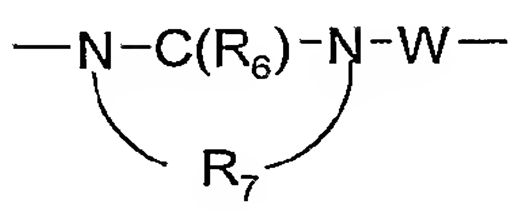
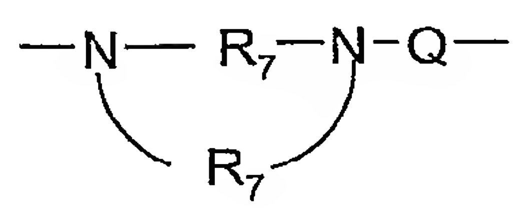
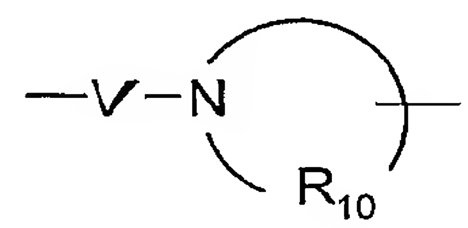
In some embodiments of Formula IX, R_1 is selected from the group consisting of methyl and 2-methylpropyl; and R_2 is methyl. In certain of these embodiments, R_{A2} and R_{B2} are each methyl.

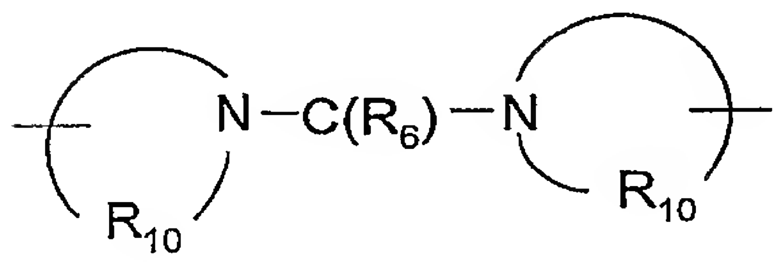
In some embodiments (e.g., of Formulas II through VII), R_3 is selected from the group consisting of -Z-R_4, -Z-X-R_4, -Z-X-Y-R_4, -Z-X-Y-X-Y-R_4, and -Z-X-R_5 wherein:

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-,

$-C(R_6)-N(OR_9)-$, $-O-N(R_8)-Q-$, $-O-N=C(R_4)-$, $-C(=N-O-R_8)-$, $-CH(-N(-O-R_8)-Q-R_4)-$,

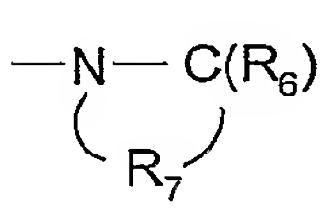
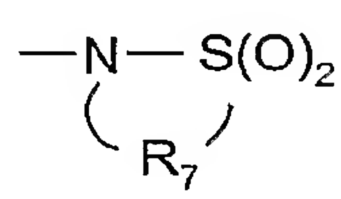
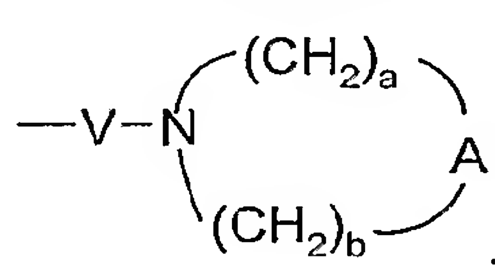
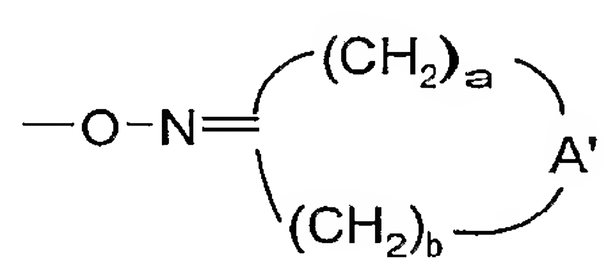
, , , , and

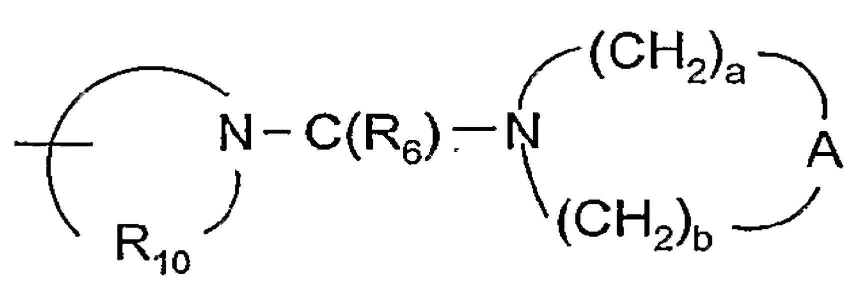
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

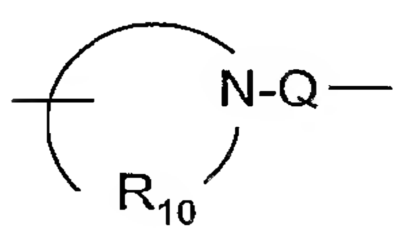
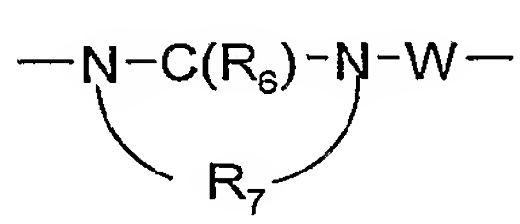
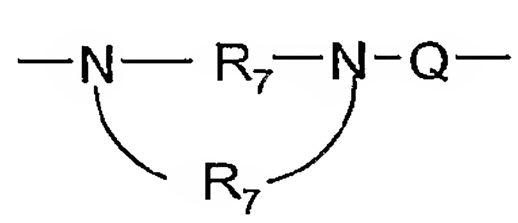
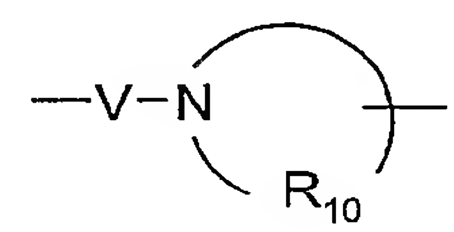
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

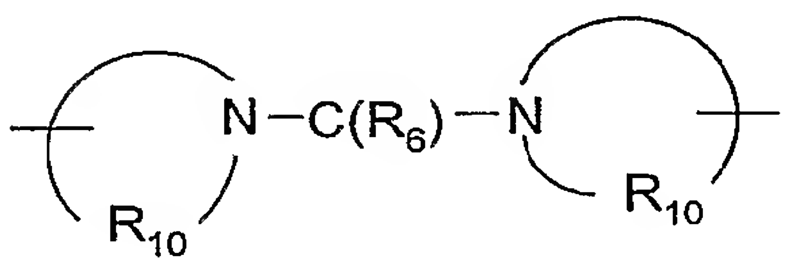
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

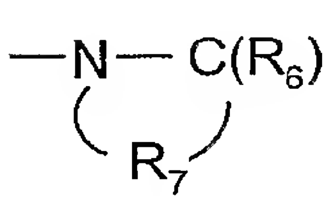
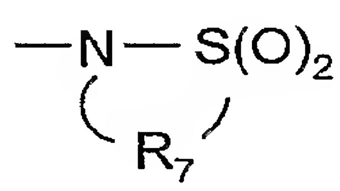
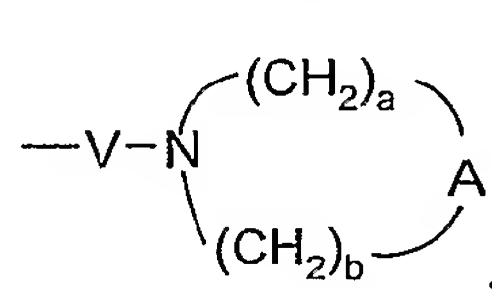
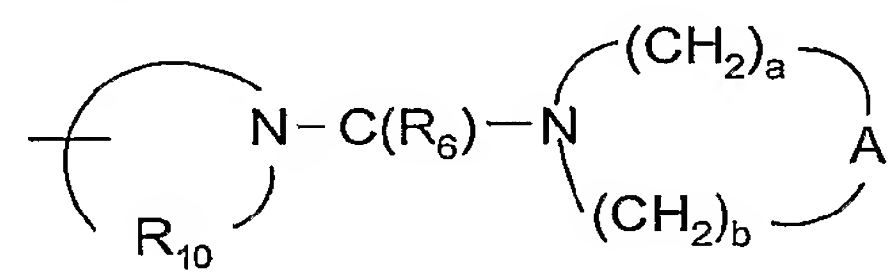
W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

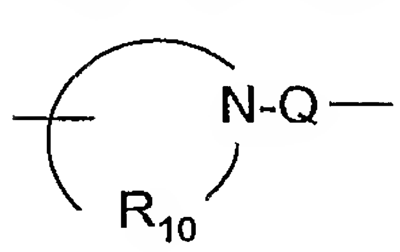
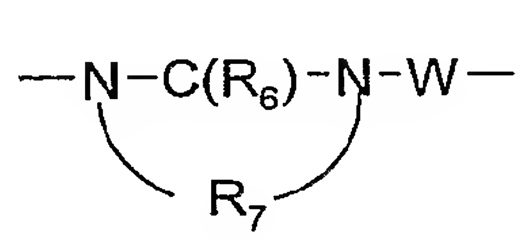
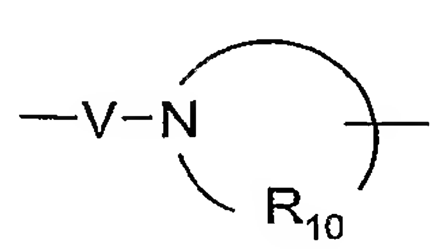
In certain of these embodiments (e.g., of Formulas II through VII), Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, -O-C(O)-O-, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,

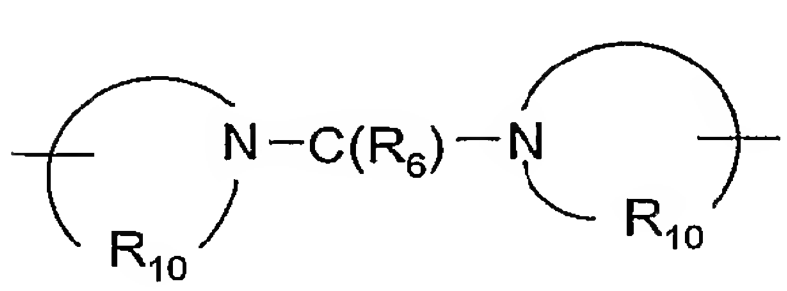
, , , , and

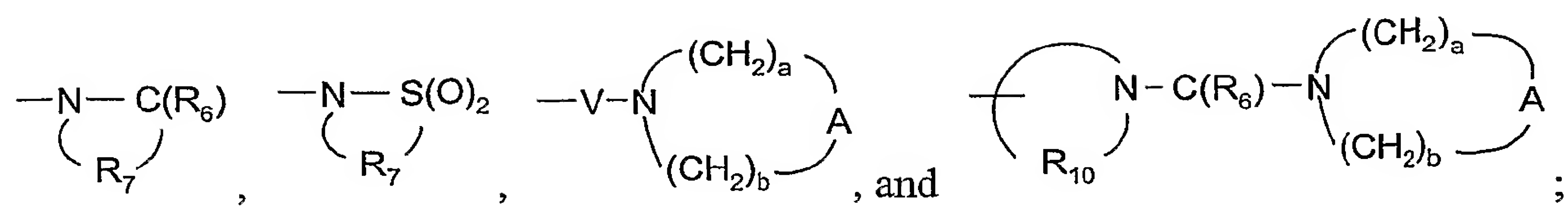
; R_5 is selected from the group consisting of

, , , and ;

and R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl. In certain of these embodiments (e.g., of Formulas II through VII), Y is selected from the group consisting of $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, -O-C(O)-O-, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$,

, , , and

; R_5 is selected from the group consisting of



R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl; and Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and -C(R_6)-N(OR_9)-.

In some embodiments (e.g., of Formulas II through VII), R_3 is at the 7-position of the pyrazoloquinoline or pyrazolonaphthyridine.

In some embodiments (e.g., of Formulas II through VII), R_3 is selected from the group consisting of aryl, arylalkyleneoxy, and heteroaryl, wherein aryl, arylalkyleneoxy, and heteroaryl are unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl and halogen. In certain of these embodiments, m is 1, and n is 0. In certain of these embodiments, R_3 is at the 7-position of the pyrazoloquinoline or pyrazolonaphthyridine.

In some embodiments (e.g., of Formulas II through VII), R_3 is selected from the group consisting of phenyl, benzyloxy, 3-furyl, pyridin-3-yl, *p*-toluyl, (4-chlorobenzyl)oxy, and (4-methylbenzyl)oxy. In certain of these embodiments, m is 1, and n is 0. In certain of these embodiments, R_3 is at the 7-position of the pyrazoloquinoline or pyrazolonaphthyridine.

In some embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo. In certain of these embodiments, R_4 is alkyl, aryl, or heteroaryl.

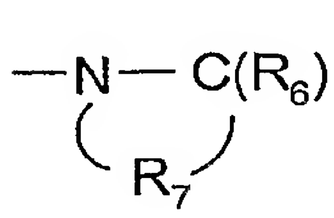
In some embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo.

In some embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, and arylalkenylenyl, wherein the alkyl, aryl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo.

In some embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, heterocyclyl, and heteroaryl, wherein the alkyl, aryl, aryloxyalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, and in the case of heterocyclyl, oxo.

In some embodiments, R_4 is alkyl, aryl, or heteroaryl. In certain embodiments, R_4 is alkyl. In certain embodiments, R_4 is aryl. In certain embodiments, R_4 is heteroaryl.

In some embodiments, R_5 is selected from the group consisting of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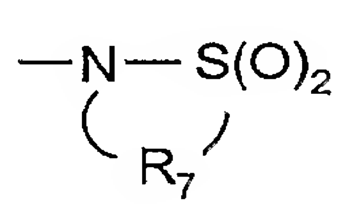
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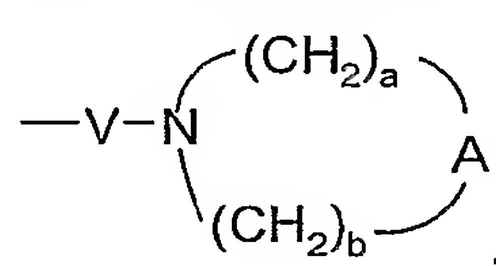
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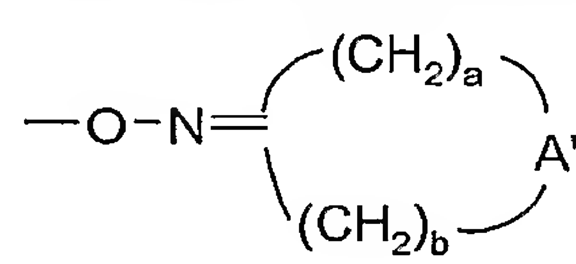
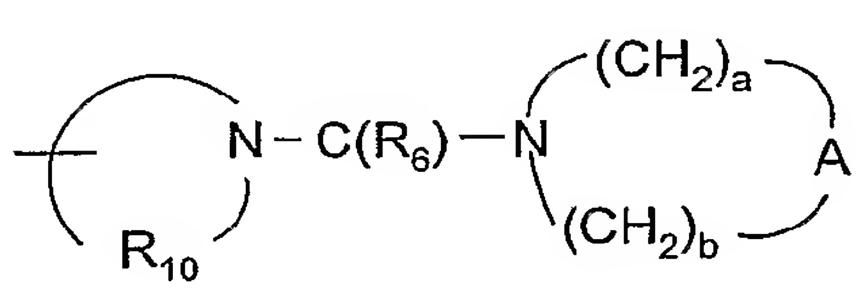
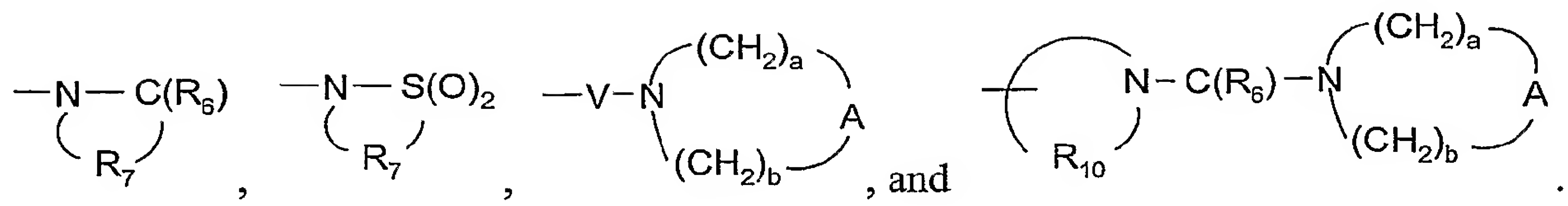
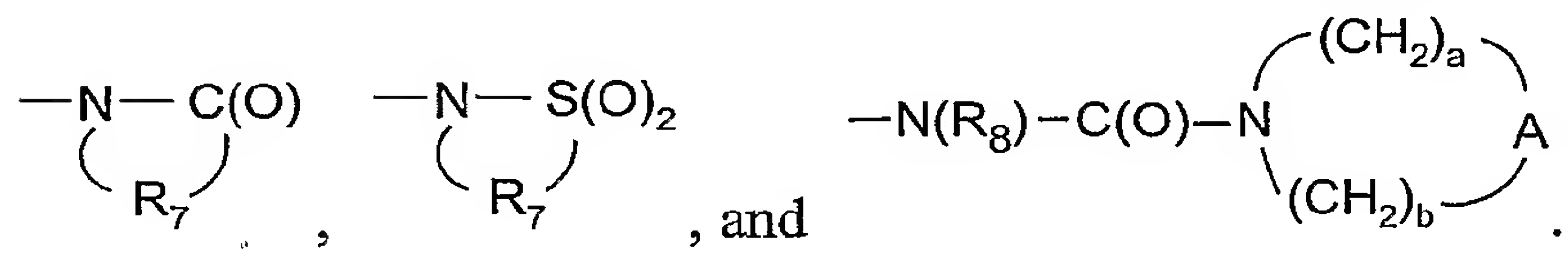

, and


.

In some embodiments, R_5 is selected from the group consisting of



In some embodiments, R_5 is selected from the group consisting of



In some embodiments, R_6 is selected from the group consisting of =O and =S. In certain embodments, R_6 is =O. In certain embodiments, R_6 is =S.

In some embodiments, R_7 is C_{2-7} alkylene. In certain embodiments, R_7 is C_{3-4} alkylene.

In some embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl. In certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl. In certain embodiments, R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, and arylalkylenyl. In certain embodiments, R_8 is hydrogen, alkyl, or hydroxyalkylenyl. In certain embodiments, R_8 is hydrogen. In certain embodiments, R_8 is alkyl.

In some embodiments, R_9 is selected from the group consisting of hydrogen and alkyl. In certain embodiments, R_9 is alkyl. In certain embodiments, R_9 is hydrogen.

In some embodiments, R_{10} is C_{3-8} alkylene. In certain embodiments, R_{10} is C_{4-5} alkylene.

In some embodiments, A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, and –N(R_4)-. In certain embodiments, A is selected from the group consisting of -O-, -C(O)-, and –N(R_4)-. In certain embodiments, A is -O-.

In some embodiments, A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH_2-.

In some embodiments, Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-. In certain embodiments, Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, and

$-C(R_6)-N(OR_9)-$. In certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(O)-O-$, and $-C(O)-S-$. In certain embodiments, Q is selected from the group consisting of a bond, $-C(O)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-$, and $-S(O)_2-N(R_8)-$. In certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-S(O)_2-$, and $-C(R_6)-N(R_8)-W-$. In certain embodiments, Q is selected from the group consisting of a bond, $-C(O)-$, $-S(O)_2-$, and $-C(O)-N(R_8)-$.

In some embodiments, V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$. In certain embodiments, V is $-C(R_6)-$. In certain embodiments, V is $-N(R_8)-C(R_6)-$.

In some embodiments, W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$. In certain embodiments, W is selected from the group consisting of a bond and $-C(O)-$. In certain embodiments, W is a bond.

In some embodiments, X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups.

In some embodiments, X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group.

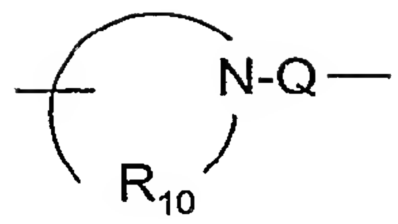
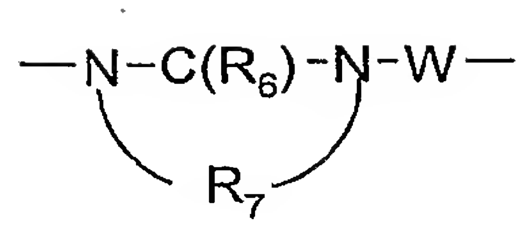
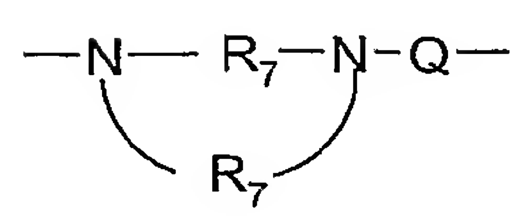
In some embodiments, X is alkylene that is optionally terminated by arylene or heterocyclylene.

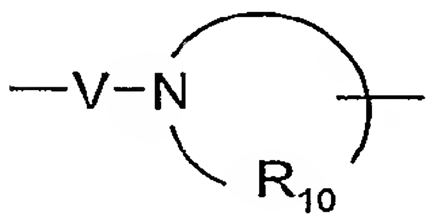
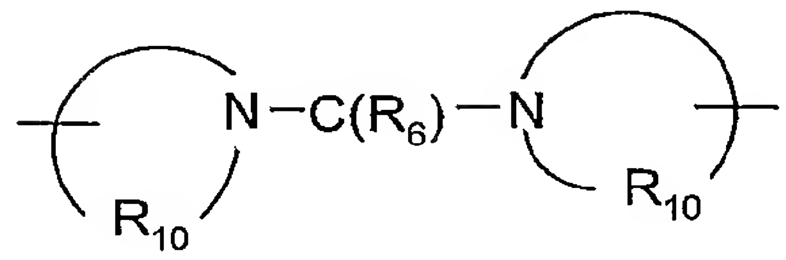
In some embodiments, X is alkylene that is optionally interrupted or terminated by heterocyclylene.

In some embodiments, X is alkylene. In certain embodiments, X is C_{1-4} alkylene.

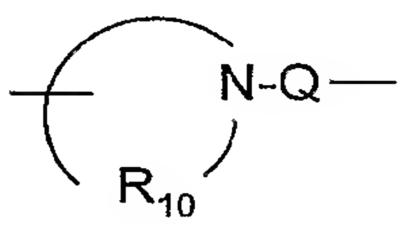
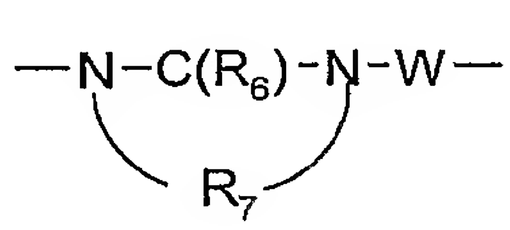
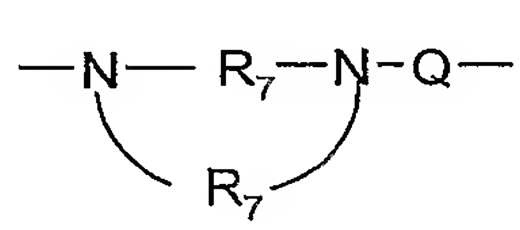
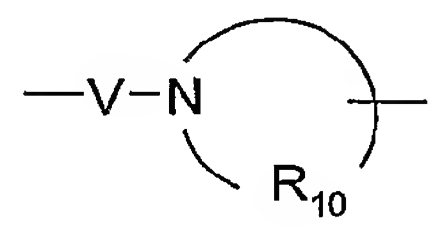
In some embodiments, X^1 is selected from the group consisting of alkylene and arylene. In certain embodiments, X^1 is alkylene. In certain embodiments, X^1 is C_{1-4} alkylene. In certain embodiments, X^1 is arylene.

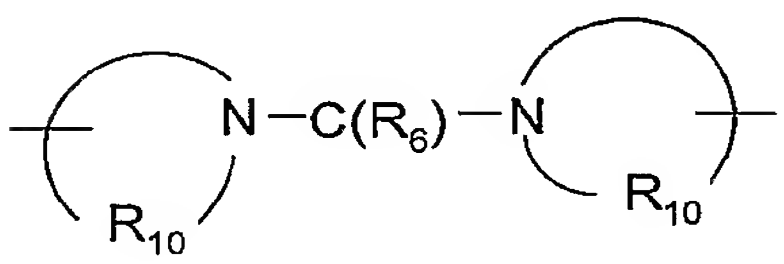
In some embodiments, Y is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, $-C(R_6)-N(OR_9)-$, $-O-N(R_8)-Q-$, $-O-N=C(R_4)-$, $-C(=N-O-R_8)-$,

-CH(-N(-O-R_8)-Q-R_4)-, , , ,

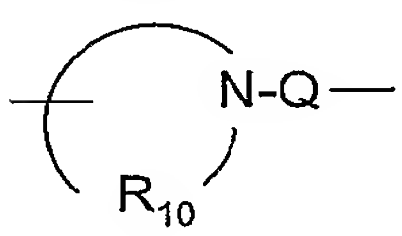
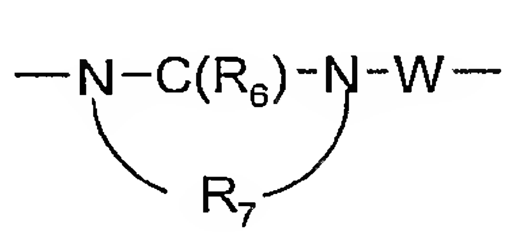
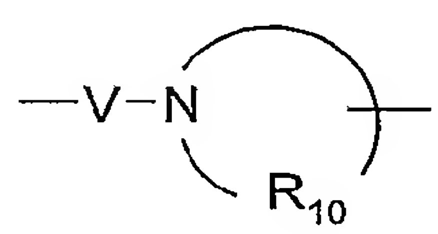
, and .

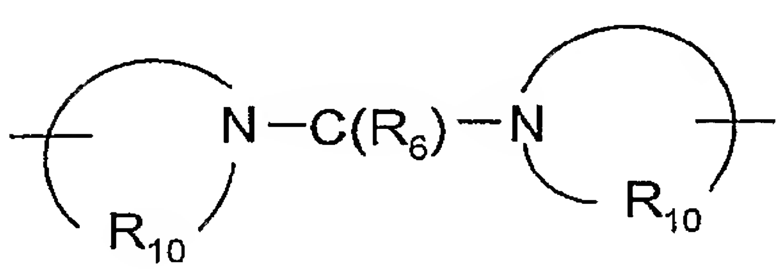
In some embodiments, Y is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,

, , , , and

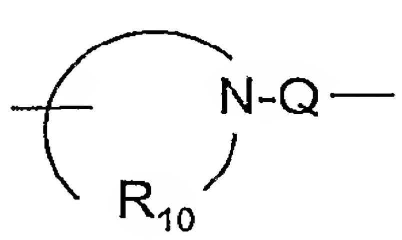
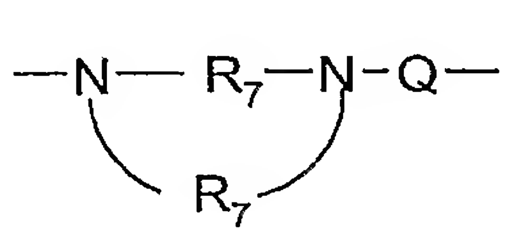
.

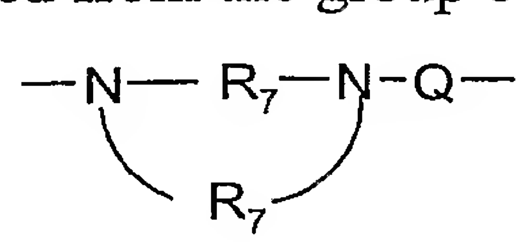
In some embodiments, Y is selected from the group consisting of -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,

, , , and

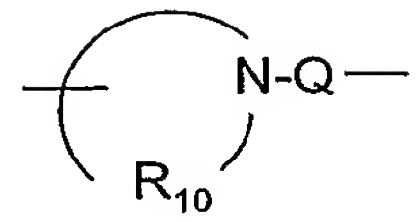
.

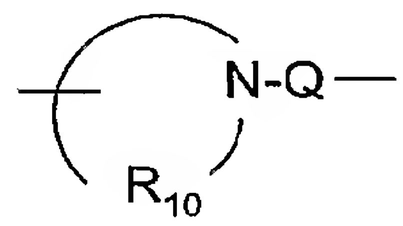
In some embodiments, Y is selected from the group consisting of -S(O)$_2$-, -S(O)$_2$-N(R_8)-, -C(O)-, -C(O)-O-, -O-C(O)-, -N(R_8)-Q-, -C(O)-N(R_8)-,

, and .

In some embodiments, Y is selected from the group consisting of -S(O)$_2$-, -C(O)-, -C(O)-O-, -N(R_8)-Q-, -C(O)-N(R_8)-, and .

In some embodiments, Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-,

-N(R_8)-C(S)-N(R_8)-, -N(R_8)-S(O)$_2$-N(R_8)-, or  .

In some embodiments, Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-C(O)-N(R_8)-, or  .

In some embodiments, Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, - S(O)$_2$- N(R_8)-, or -N(R_8)-C(O)-N(R_8)-. In certain embodiments, Y is -N(R_8)-C(O)-. In certain embodiments, Y is -N(R_8)-S(O)$_2$-. In certain embodiments, Y is - S(O)$_2$- N(R_8)-. In certain embodiments, Y is -N(R_8)-C(O)-N(R_8)-.

In some embodiments, Y^1 is selected from the group consisting of -S-, -C(O)-, -C(O)-O-, -C(O)-N(R_8)-, -S(O)$_2$-N(R_8)-, and -N(R_8)-C(O)-. In some embodiments, Y^1 is selected from the group consisting of -S-, -C(O)-, and -C(O)-O-.

In some embodiments, Z is a bond or -O-. In certain embodiments, Z is a bond. In certain embodiments, Z is -O-.

In some embodiments, a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7. In some embodiments, a and b are each the integer 2.

In some embodiments (e.g., of Formulas III-VII), n is 0, or m is 0.

In some embodiments (e.g., of Formulas III-VII), m and n are 0.

In some embodiments (e.g., of Formulas III-VII), m is 0, and n is 1.

In some embodiments (e.g., of Formulas III-VII), m is 1, and n is 0.

In some embodiments (e.g., of Formula VIII), n is 0.

Preparation of Compounds

Compounds of the invention can be prepared according to Reaction Scheme I, where R, R_1, R_2, and n are defined as above. Ketoesters of Formula X in Reaction Scheme I and their sodium salts are known and can be prepared from a variety of ketones using conventional methods, such as the Claisen condensation, Claisen, L., *Berichte*, *42*, 59 (1909).

Numerous functionalized ketones useful as Claisen condensation starting materials are commercially available; others can be prepared by known methods. For example, *tert*-

butyl 1,1-dimethyl-3-oxobutylcarbamate, also called (1,1-dimethyl-3-oxobutyl)carbamic acid *tert*-butyl ester, has been reported, Peschke, B. *et al*, *Eur. J. Med. Chem.*, *34*, pp. 363-380, (1999). In another example, 4-(propylthio)butan-2-one can be prepared by combining 1-propanethiol and 4-chloro-2-butanone at ambient temperature in the presence of sodium hydride in a suitable solvent such as tetrahydrofuran (THF) and isolating the product using conventional methods. In a third example, a Michael addition can be carried out with phenyl vinyl sulfone and a carbanion generated from methyl acetoacetate and sodium methoxide. The resulting Michael adduct can be decarboxylated under acidic conditions, for example hydrochloric acid in methanol, to provide 5-(phenylsulfonyl)pentan-2-one.

In step (1) of Reaction Scheme I, a sodium salt of a compound of Formula X reacts with a hydrazine of Formula R_2NHNH_2 to provide a pyrazole carboxylate of Formula XI. The reaction is conveniently carried out by slowly adding the hydrazine to a solution of the salt of a compound of Formula X in a suitable solvent such as acetic acid. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

If step (1) is carried out using hydrazine, the resulting pyrazole carboxylate of Formula XI where R_2 is hydrogen can be alkylated using known synthetic methods, Auwers, K. v., Hollman, H., *Berichte*, *59*, 606 (1926), to provide a pyrazole carboxylate of Formula XI where R_2 is defined as above. The alkylation is conveniently carried out by treating a solution of the pyrazole carboxylate of Formula XI, where R_2 is hydrogen, with a base such as sodium ethoxide followed by an alkylating agent of Formula R_2-Halide. The reaction is run in a suitable solvent such as ethanol and can be carried out at an elevated temperature, for example, the reflux temperature of the solvent, or at ambient temperature. Numerous reagents of Formula R_2-Halide are commercially available; others can be prepared using known synthetic methods. The pyrazole carboxylate of Formula XI can be isolated from the reaction and separated from its isomer using conventional methods.

In step (2) of Reaction Scheme I, the ester group of a pyrazole carboxylate of Formula XI is converted to an amide. The amination is conveniently carried out by adding ammonium hydroxide to the pyrazole carboxylate of Formula XI in a suitable solvent such as methanol and heating at an elevated temperature such as 100 °C. The reaction can be

carried out in a pressure vessel. The resulting pyrazole carboxamide of Formula XII can be isolated using conventional methods.

Alternatively, step (2) can be carried out by first hydrolyzing a pyrazole carboxylate of Formula XI to a carboxylic acid and then converting the carboxylic acid to an amide. The ester hydrolysis can be carried out under basic conditions by combining a pyrazole carboxylate of Formula XI with lithium hydroxide or sodium hydroxide in water and in a suitable solvent such as methanol or ethanol. The reaction can be carried out at ambient temperature, and the carboxylic acid product can be isolated using conventional methods. The conversion of the carboxylic acid to a pyrazole carboxamide of Formula XII can be carried out by first treating the carboxylic acid with oxalyl chloride at ambient temperature in a suitable solvent such as dichloromethane to generate an acid chloride, which can then be treated with ammonium hydroxide at a sub-ambient temperature such as 0 °C. Alternatively, the conversion of the carboxylic acid to a pyrazole carboxamide of Formula XII can be carried out under coupling conditions by adding 1-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride to a solution of the carboxylic acid in a suitable solvent such as *N,N*-dimethylformamide (DMF) at ambient temperature and then adding concentrated ammonium hydroxide. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme I, a pyrazole carboxamide of Formula XII is dehydrated to a pyrazole carbonitrile of Formula XIII. Suitable dehydrating agents include thionyl chloride, trifluoroacetic anhydride, and phosphorous oxychloride. The reaction is conveniently carried out by treating the pyrazole carboxamide of Formula XII with phosphorous oxychloride and heating the reaction at an elevated temperature such as 90 °C. The reaction can also be carried out by combining the pyrazole carboxamide of Formula XII with trifluoroacetic anhydride in the presence of a base such as triethylamine and in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as 0 °C. The product can be isolated using conventional methods.

In step (4) of Reaction Scheme I, a pyrazole carbonitrile of Formula XIII is brominated to provide a bromo-substituted pyrazole carbonitrile of Formula XIV. The bromination is conveniently carried out by adding bromine to a solution of the pyrazole

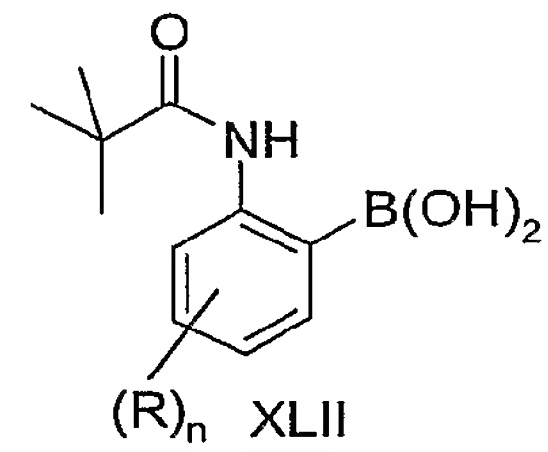
carbonitrile of Formula XIII and potassium acetate in acetic acid. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (5) of Reaction Scheme I, a bromo-substituted pyrazole carbonitrile of Formula XIV undergoes a transition-metal catalyzed cross coupling reaction with a reagent of Formula XV to form a pyrazole-substituted aniline of Formula XVI. Reagents of Formula XV, where M is, for example, $-B(OH)_2$, $-B(O\text{-alkyl})_2$, $-Sn(alkyl)_3$, and -Zn-Halide, are known to undergo coupling reactions. Several reagents of Formula XV are commercially available; others can be prepared using known synthetic methods. For example, *tert*-butoxycarbonyl (Boc)-protected anilines undergo directed ortho metalation in the presence of butyllithium reagents. The resulting organolithium intermediate reacts with electrophiles such as $B(O\text{-alkyl})_3$ and $ClSn(alkyl)_3$ to provide compounds of Formula XV, where M is $-B(O\text{-alkyl})_2$ or $-B(OH)_2$ and $-Sn(alkyl)_3$, respectively, after removal of the Boc protecting group.

In step (5), a Suzuki coupling reaction is conveniently carried out by heating a mixture of the bromo-substituted pyrazole carbonitrile of Formula XIV, palladium (II) acetate, triphenylphosphine, and a boron reagent of Formula XV, where M is $-B(OH)_2$ or $-B(O\text{-alkyl})_2$, in the presence of a base such as sodium carbonate. The reaction is carried out in a suitable solvent or solvent mixture such as n-propanol:water and can be heated at an elevated temperature such as 100 °C. The product can be isolated using conventional methods.

In step (6) of Reaction Scheme I, the amine and nitrile functionalities of a pyrazole-substituted aniline of Formula XVI react under acidic conditions to form a pyrazolo[3,4-*c*]quinoline of Formula XVII, a subgenus of Formulas I, II, III, and Ia. The intramolecular addition is conveniently carried out by stirring acetyl chloride in ethanol and adding the resulting acidic solution to the pyrazole-substituted aniline of Formula XVI. The reaction is then heated at reflux to provide the pyrazolo[3,4-*c*]quinoline of Formula XVII. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, in steps (5) and (6) of Reaction Scheme I, a bromo-substituted pyrazole carbonitrile of Formula XIV undergoes a Suzuki coupling with a reagent of Formula XLII.



XLII

Some compounds of Formula XLII are known or can be prepared by known synthetic methods; see, Rocca, P. *et al*, *Tetrahedron*, 49, pp. 49-64 (1993). The Suzuki coupling reaction can be carried out according to the method described above. The resulting pivaloylamino-substituted compound undergoes a base-promoted intramolecular cyclization in step (6) of Reaction Scheme I and subsequent cleavage of the pivaloyl group to provide a pyrazolo[3,4-*c*]quinoline of Formula XVII. The reaction is conveniently carried out by heating the pivaloylamino-substituted coupling product with potassium *tert*-butoxide in a suitable solvent such as ethanol at an elevated temperature such as the reflux temperature of the solvent. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

For some embodiments, compounds in Reaction Scheme I can be further elaborated using conventional synthetic methods. For example, R_1 can be a 2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl group if *tert*-butyl 1,1-dimethyl-3-oxobutylcarbamate is used as the starting ketone to make the ketoester of Formula X. The *tert*-butoxycarbonyl group is removed under the acidic cyclization conditions described in step (6) to provide a 2-amino-2-methylpropyl group, which can be converted to an amide, a sulfonamide, a sulfamide, or a urea using the methods described below in step (11) of Reaction Scheme VII.

In another example, an olefin-containing R_1 group may be oxidized to an epoxide by conventional methods. The oxidation is conveniently carried out prior to step (4) of Reaction Scheme I by adding 3-chloroperoxybenzoic acid to a solution of a pyrazole carbonitrile of Formula XIII, which contains an olefin substituent, in a suitable solvent such as dichloromethane. The reaction may be carried out at ambient temperature, and the product can be isolated by conventional methods. The epoxide can be opened during the

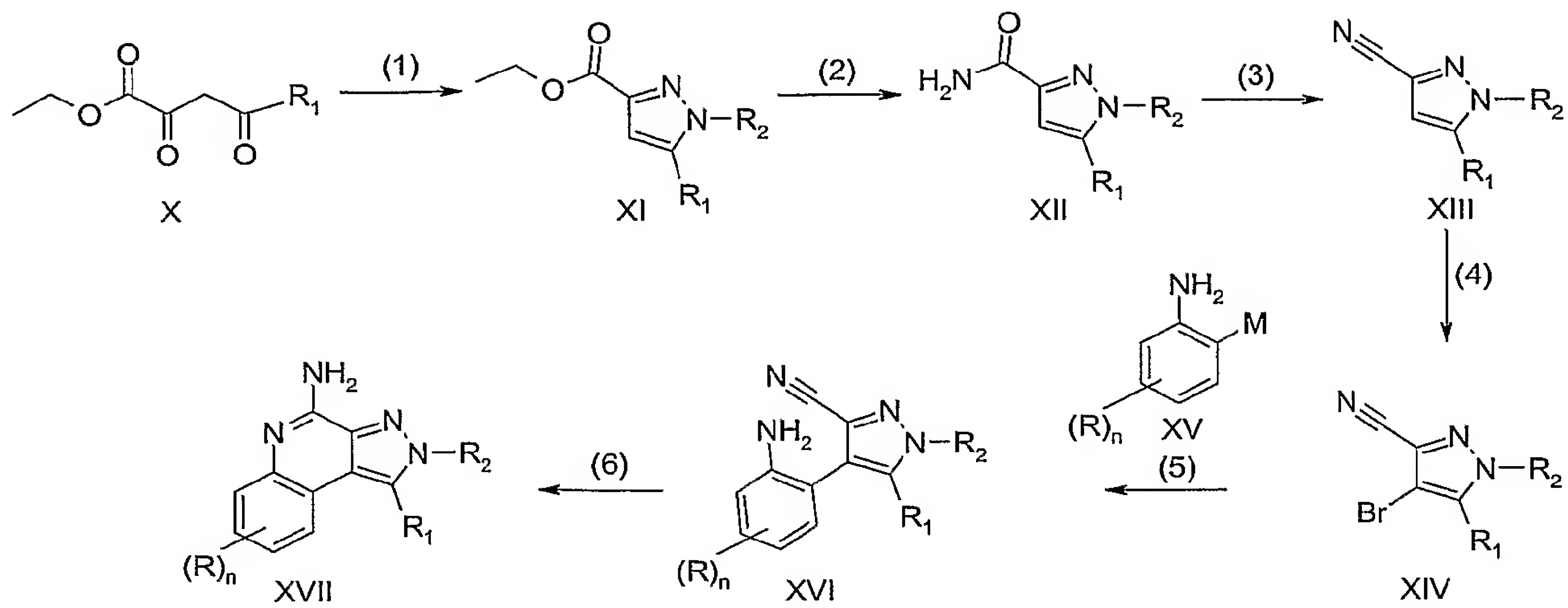
bromination in step (4) by combining the compound of Formula XIII, which contains an epoxide substituent, with two equivalents of bromine in acetic acid at ambient temperature to provide a compound of Formula XIV substituted at R_1 with a vicinal bromohydrin. The bromohydrin may then be reduced under free radical conditions to provide a compound of Formula XIV substituted with a hydroxyalkyl group. The reduction may be carried out by adding tributyltin hydride and azobisisobutyronitrile at ambient temperature to a bromohydrin-substituted compound of Formula XIV in a suitable solvent such as toluene. The product may be isolated by conventional methods and then subjected to steps (5) and (6) of Reaction Scheme I. Using these methods an R_1 2-methylpropenyl group can be converted into a 2-hydroxy-2-methylpropyl group.

A hydroxy group introduced at the R_1 position according to the above method can be treated with sodium hydride to form an alkoxide, which is reacted with a vinyl sulfone of Formula CH_2=CH-S(O)$_2$-R_4 to provide a compound in which R_1 is -X-Y-R_4, wherein Y is

-SO_2-. The reaction can be carried out by adding catalytic sodium hydride dispersed in mineral oil to a solution of a compound of Formula XIV, wherein R_1 has hydroxy group, and a vinyl sulfone in a suitable solvent such DMF or tetrahydrofuran. The reaction can be run at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated by conventional methods and then subjected to steps (5) and (6) of Reaction Scheme I. Many vinyl sulfones are commercially available or can be prepared using known synthetic methods. These methods can be used to provide a compound of Formula XVII, wherein R_1 is a 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl group.

In another example, R_1 can be -X-Y-R_4, wherein Y is -S-. The thioether group may be oxidized to a sulfone prior to step (2) of Reaction Scheme I to provide a compound where R_1 is -X-Y-R_4 and Y is -SO_2-. The oxidation is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a pyrazole carboxylate of Formula XI in a suitable solvent such as dichloromethane or chloroform. The product may be isolated by conventional methods and then subjected to steps (2) through (6) of Reaction Scheme I.

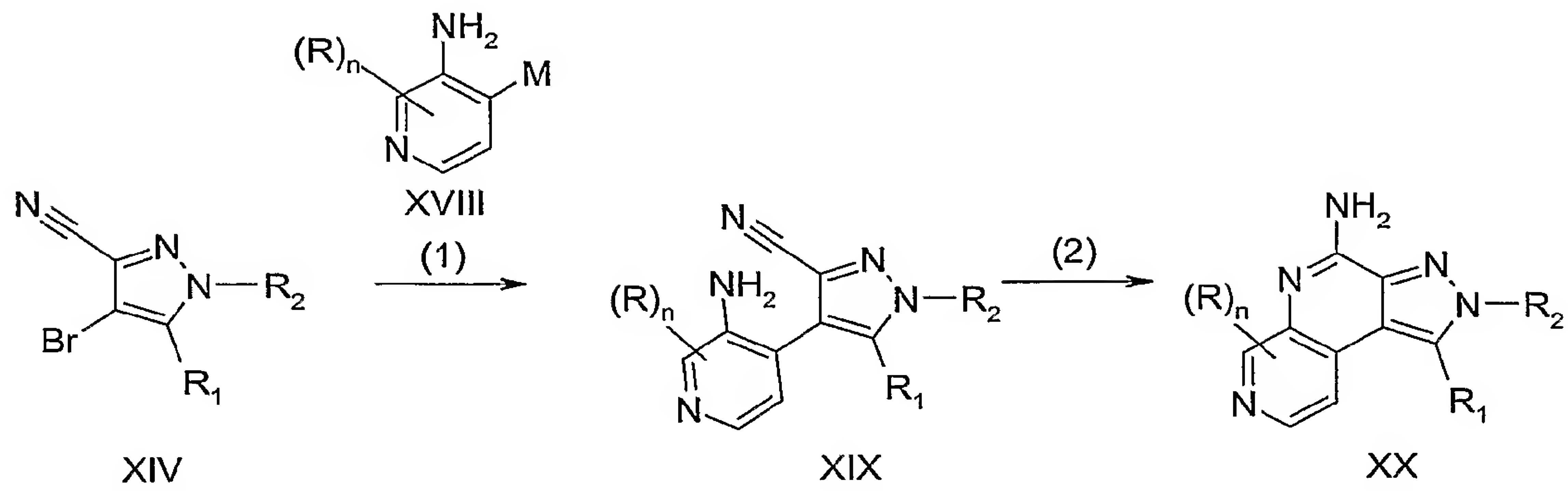
Reaction Scheme I



Pyrazolo[3,4-*c*]naphthyridines of the invention can be prepared according to Reaction Scheme II, where R, R_1, R_2, and n are as defined above. In step (1) of Reaction Scheme II, a bromo-substituted pyrazole carbonitrile of Formula XIV undergoes a transition-metal catalyzed cross coupling reaction with a reagent of Formula XVIII or a positional isomer thereof, where M is as defined above, to form a pyrazole-substituted aminopyridine of Formula XIX. Reagents of Formula XVIII and its isomers can be prepared using known methods, for example, by directed ortho metalation of Boc-protected aminopyridines and subsequent electrophilic substitution. Alternatively, for some isomers, halogen-lithium exchange and subsequent electrophilic substitution can be used. For example, halogen-lithium exchange can be carried out on a 2-bromopyridine that has a protected amino group in the 3-position; subsequent electrophilic substitution with tributyltin chloride and deprotection of the amino group provides 3-amino-2-tri-*n*-butylstannylpyridine, a useful reagent for step (1) of Reaction Scheme II. The coupling reaction in step (1) of Reaction Scheme II can be carried out as described for step (5) of Reaction Scheme I.

In step (2) of Reaction Scheme II, the amine and nitrile functionalities of a pyrazole-substituted aminopyridine of Formula XIX react under acidic conditions to form a pyrazolo[3,4-*c*]naphthyridine of Formula XX, a subgenus of Formulas I, II, VI, and Ia, or an isomer thereof. Step (2) of Reaction Scheme II can be carried out as described for step (6) of Reaction Scheme I, and the product can be isolated by conventional methods.

Reaction Scheme II



Compounds of the invention can also be prepared according to Reaction Scheme III, where n is defined as above and R_a, R_{1a}, and R_{2a} are subsets of R, R_1, and R_2 as defined above that do not include those substituents which one skilled in the art would recognize as being susceptible to oxidation in step (5). These susceptible substituents include -S- or heteroaryl groups.

Acetals of Formula XXI are reported in the literature and can be prepared using known synthetic methods, Royals, E. E., Robinson, A. G. III, *J. Am. Chem. Soc.*, *78*, 4161 (1956). For example, a ketone of Formula $CH_3C(O)R_{1a}$ can be condensed with ethyl diethoxyacetate under Claisen condensation conditions to provide an acetal of Formula XXI. The reaction is conveniently carried out by adding sodium *tert*-butoxide to a solution of ethyl diethoxyacetate and the ketone of Formula $CH_3C(O)R_{1a}$ in ethanol and heating the reaction at reflux. Numerous ketones of Formula $CH_3C(O)R_{1a}$ are commercially available. Others can be readily prepared using known synthetic methods. Amido ketones can be prepared according to the literature procedure, Ritter, J. J. and Minieri, P. P., *J. Am . Chem. Soc.*, *70*, 4045, (1948) by adding a nitrile of Formula R_4-CN to an α,β-unsaturated ketone under acidic conditions.

In step (1) of Reaction Scheme III, an acetal of Formula XXI is reacted with a hydrazine of Formula R_{2a}-NH-NH_2 to provide a pyrazole of Formula XXII. The reaction is conveniently carried out by slowly adding the hydrazine to a solution of an acetal of Formula XXI in a suitable solvent such as ethanol. The reaction can be run at ambient temperature, and the product can be isolated using conventional methods.

In step (2) of Reaction Scheme III, the acetal in the pyrazole of Formula XXII is converted to an aldehyde under acidic conditions. The reaction is conveniently carried out by treating the acetal-substituted pyrazole of Formula XXII with hydrochloric acid in a suitable solvent such as tetrahydrofuran. The reaction can be carried out at ambient temperature to provide an aldehyde-substituted pyrazole of Formula XXIII. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme III, a pyrazole of Formula XXIII is brominated to provide a bromo-substituted pyrazole of Formula XXIV. The reaction can be carried out as described in step (4) of Reaction Scheme I.

In step (4) of Reaction Scheme III, a bromo-substituted pyrazole of Formula XXIV undergoes a transition-metal catalyzed cross coupling reaction with a reagent of Formula XV, where M is defined as above. The reaction is conveniently carried out using the Suzuki reaction conditions described in step (5) of Reaction Scheme I. Under these reaction conditions, intramolecular condensation of the amine with the aldehyde group takes place to form a pyrazolo[3,4-*c*]quinoline of Formula XXV. The product can be isolated using conventional methods.

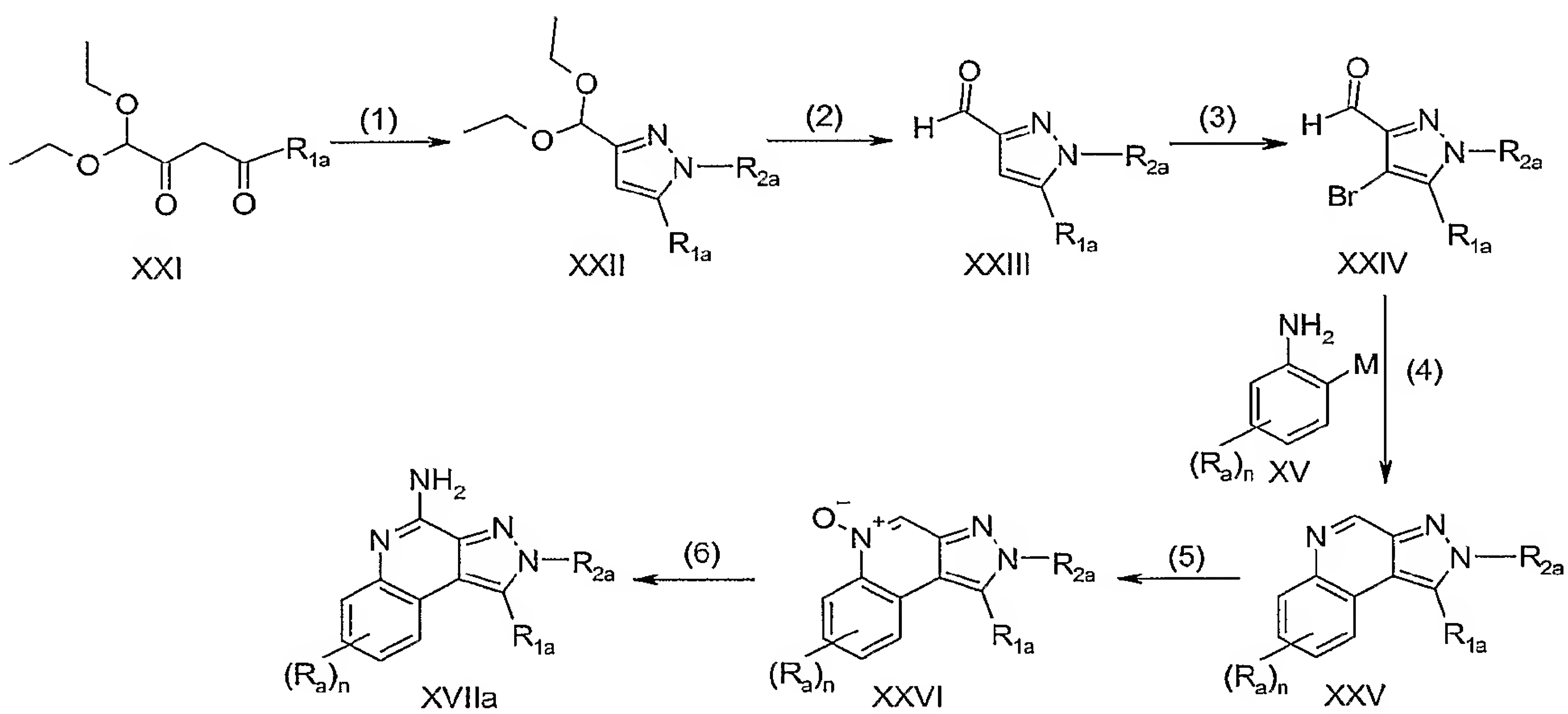
In step (5) of Reaction Scheme III, a pyrazolo[3,4-*c*]quinoline of Formula XXV is oxidized to provide a pyrazolo[3,4-*c*]quinoline-5*N*-oxide of Formula XXVI using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXV in a solvent such as dichloromethane or chloroform. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (6) of Reaction Scheme III, a pyrazolo[3,4-*c*]quinoline-5*N*-oxide of Formula XXVI is aminated to provide a pyrazolo[3,4-*c*]quinolin-4-amine of Formula XVIIa, a subgenus of Formulas I, II, III, and Ia. Step (6) can be carried out by the activation of an *N*-oxide of Formula XXVI by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by

adding ammonium hydroxide to a solution of the *N*-oxide of Formula XXVI in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively step (6) can be carried out by the reaction of a pyrazolo[3,4-*c*]quinoline-5*N*-oxide of Formula XXVI with trichloroacetyl isocyanate followed by base-promoted hydrolysis of the resulting intermediate to provide a pyrazolo[3,4-*c*]quinolin-4-amine of Formula XVIIa. The reaction is conveniently carried out in two steps by (i) adding trichloroacetyl isocyanate to a solution of the *N*-oxide of Formula XXVI in a solvent such as dichloromethane and stirring at ambient temperature to provide an isolable amide intermediate. In step (ii), a solution of the intermediate in methanol is treated with a base such as sodium methoxide at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme III

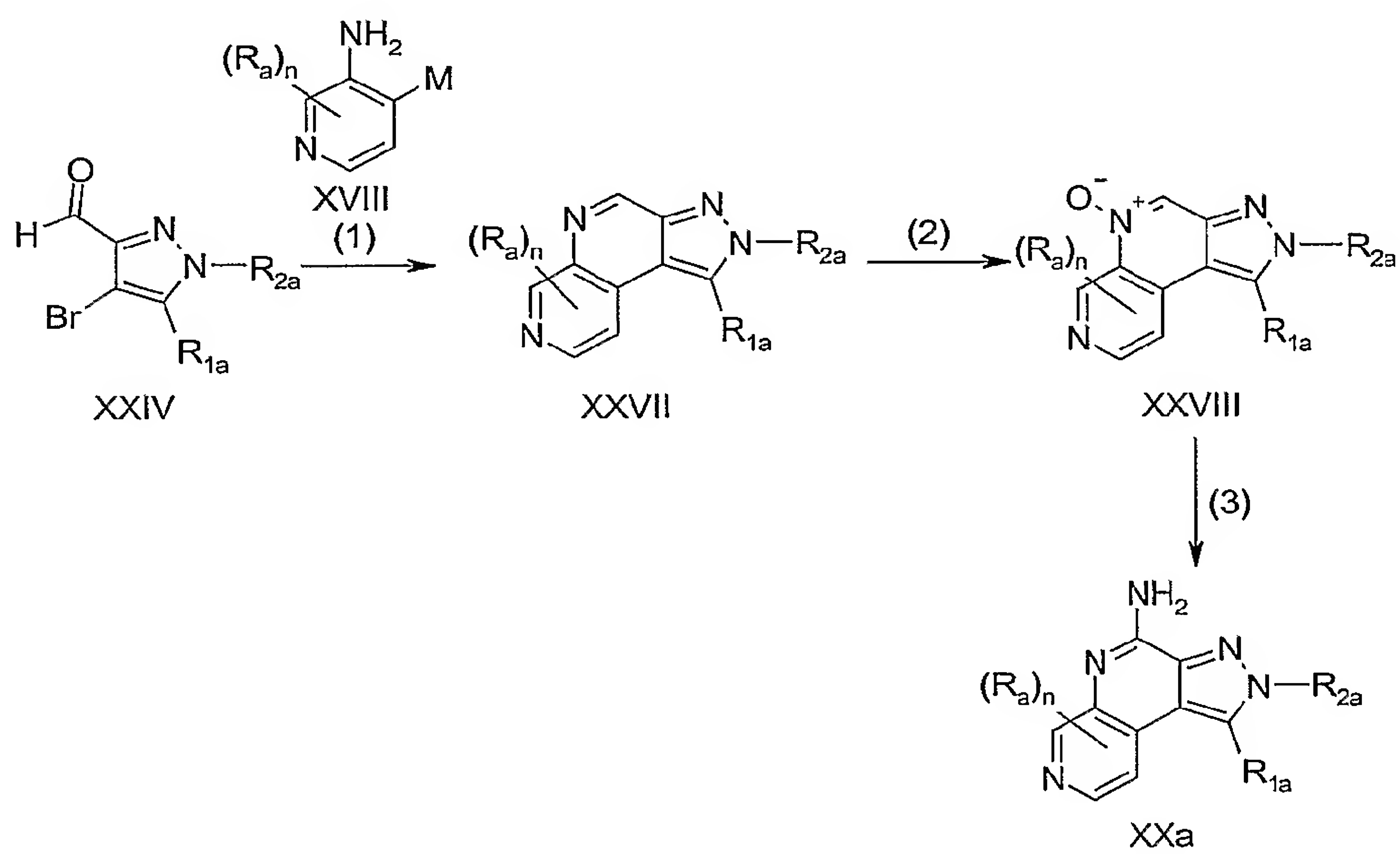


Pyrazolo[3,4-*c*]naphthyridines of the invention can be prepared according to Reaction Scheme IV, where R_a, R_{1a}, R_{2a}, and n are as defined above. In step (1) of Reaction Scheme IV, a bromo-substituted pyrazole of Formula XXIV undergoes a transition-metal catalyzed cross coupling reaction with a reagent of Formula XVIII, where M is defined as above, or one of its isomers. Step (1) of Reaction Scheme IV can be

carried out as described for step (5) of Reaction Scheme I, and under these reaction conditions an intramolecular addition can take place to provide the pyrazolo[3,4-*c*]naphthyridine of Formula XXVII.

In step (2) of Reaction Scheme IV, a pyrazolo[3,4-*c*]naphthyridine of Formula XXVII is oxidized to a pyrazolo[3,4-*c*]naphthyridine-5*N*-oxide of Formula XXVIII, which is aminated in step (3) to provide a pyrazolo[3,4-*c*]naphthyridin-4-amine of Formula XXa, a subgenus of Formulas I, II, VI, and Ia, or an isomer thereof. Steps (2) and (3) of Reaction Scheme IV can be carried out as described for steps (5) and (6), respectively, of Reaction Scheme III.

Reaction Scheme IV

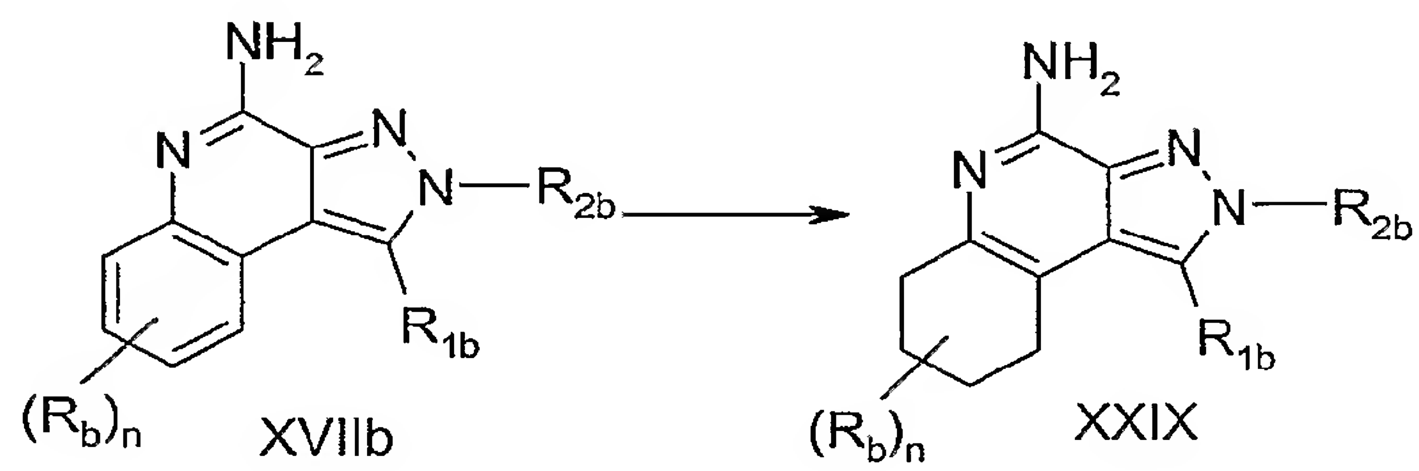


Tetrahydroquinolines of the invention may be prepared according to Reaction Scheme V, where n is as defined above and R_b, R_{1b}, and R_{2b} are subsets of R, R_1, and R_2 as defined above that do not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of the reaction. These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents. However, a compound of Formula XVII bearing an aryl substituent at R_1, for example, may be used as a substrate in the reaction to

provide a compound of Formula XXIX where the aryl group is reduced. In this manner, a phenylethyl group at R_1 may be converted to a cyclohexylethyl group.

As shown in Reaction Scheme V, a pyrazolo[3,4-c]quinolin-4-amine of Formula XVIIb can be reduced to a 6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine of Formula XXIX, a subgenus of Formulas I, II, VIII, and Ia. The reaction may be carried out under heterogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution or suspension of the compound of Formula XVIIb in a suitable solvent such as trifluoroacetic acid and placing the reaction under hydrogen pressure. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme V



Pyrazolo[3,4-*c*]pyridines of the invention can be prepared according to Reaction Scheme VI, where R_1, R_2, R_{A2}, and R_{B2} are as defined above. In step (1) of Reaction Scheme VI, a bromo-substituted pyrazole carbonitrile of Formula XIV undergoes a Sonogashira coupling reaction with (trimethylsilyl)acetylene to provide a pyrazole carbonitrile of Formula XXX. The reaction can be carried out according to the literature procedure, Sonogashira, K.; Tohda, Y.; Hagihara, N., *Tetrahedron Lett.*, 4467 (1975).

Alternatively, an iodo-substituted pyrazole carbonitrile of Formula XIVa may be used as a starting material for Reaction Scheme VI. A compound of Formula XIVa is prepared from a pyrazole carbonitrile of Formula XIII, shown in Reaction Scheme I. The iodination is conveniently carried out by treating a pyrazole carbonitrile of Formula XIII with iodine monochloride in a suitable solvent such as dichloromethane in the presence of a base such as potassium carbonate. The reaction can be carried out at ambient temperature, and the product can be isolated by conventional methods.

In step (2) of Reaction Scheme VI, the trimethylsilyl group of the pyrazole of Formula XXX is removed to provide the pyrazole of Formula XXXI. Potassium carbonate

in methanol or tetrabutylammonium fluoride in tetrahydrofuran can be used to carry out the transformation.

In step (3) of Reaction Scheme VI, the acetylene of the pyrazole of Formula XXXI is alkylated using conventional synthetic methods, Jacobs, T. L. in *Organic Reactions*, *5*, 1, (1949), to provide a pyrazole of Formula XXXII. The reaction can be carried out by deprotonation of the compound of Formula XXXI with a base and reaction of the resulting carbanion with an electrophile of Formula R_{B2}-Halide, for example, iodomethane. Step (3) can be omitted when R_{B2} is hydrogen.

For some embodiments, steps (1) through (3) of Reaction Scheme VI may be replaced with one step from a compound of Formula XIVa using a Sonogashira coupling reaction. The coupling is conveniently carried out by combining an alkyne of Formula R_{B2}-C≡C-H, copper(I) iodide, dichlorobis(triphenylphosphine)palladium(II), and triethylamine in a suitable solvent such as acetonitrile and then heating at an elevated temperature, such as the reflux temperature of the solvent. The product of Formula XXXII can be isolated using conventional methods.

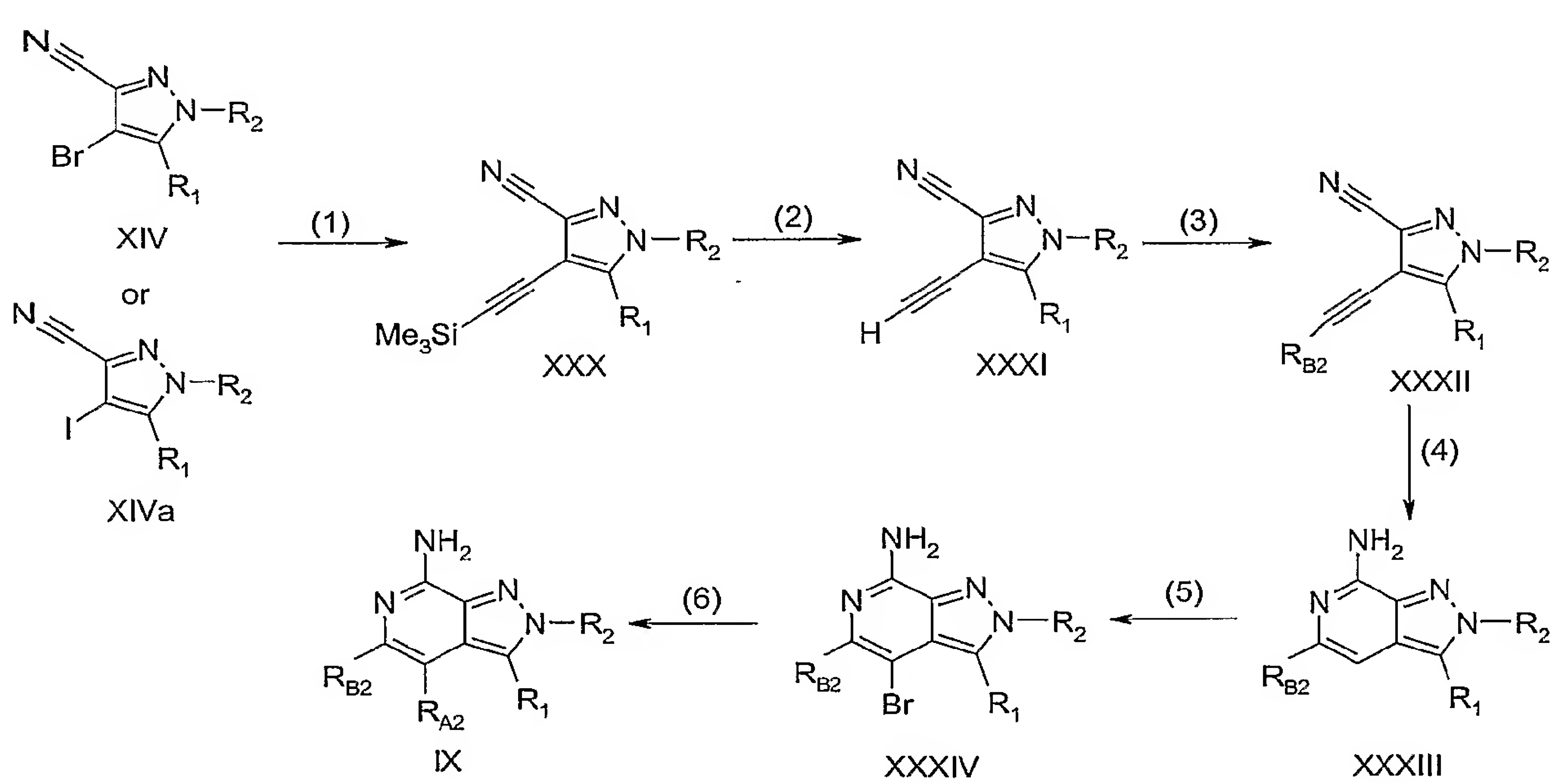
In step (4) of Reaction Scheme VI, a pyrazole of Formula XXXII reacts with ammonia to provide a pyrazolo[3,4-*c*]pyridin-4-amine of Formula XXXIII, a subgenus of Formulas I, II, IX, and Ia. The reaction can be carried out by adding a solution of ammonia in methanol to the pyrazole of Formula XXXII and heating at an elevated temperature, such as 150 °C. The reaction may be carried out in a pressure vessel. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Steps (5) and (6) may be carried out to provide a compound of Formula IX in which R_{A2} is other than hydrogen. In step (5) of Reaction Scheme VI, a pyrazolo[3,4-*c*]pyridin-4-amine of Formula XXXIII is brominated under conventional bromination conditions to provide a bromo-substituted pyrazolo[3,4-*c*]pyridin-4-amine of Formula XXXIV, a subgenus of Formulas I, II, IX, and Ia. The reaction can be carried out as described in step (4) of Reaction Scheme I.

In step (6) of Reaction Scheme VI, a bromo-substituted pyrazolo[3,4-*c*]pyridin-4-amine of Formula XXXIV undergoes a transition metal catalyzed coupling reaction with a reagent of Formula R_{A2}-M, where R_{A2} is alkenyl, alkoxy, and -N$(R_9)_2$ to provide a

pyrazolo[3,4-*c*]pyridin-4-amine of Formula IX. Reagents of Formula R_{A2}-M, where M is, for example, -B(OH)$_2$, -B(O-alkyl)$_2$, -Sn(alkyl)$_3$, and -Zn-Halide, are known to undergo coupling reactions. The transformation can be carried out by first protecting the amino group of the compound of Formula XXXIV, treating the protected compound with a reagent of Formula R_{A2}-M in the presence of a transition metal catalyst using conditions described in step (5) of Reaction Scheme I, and deprotecting the amine to provide the pyrazolo[3,4-*c*]pyridin-4-amine of Formula IX. Alternatively, step (6) can be carried out by coupling a compound of Formula XXXIV with an alkyne under Sonogashira conditions as described in step (1) of this reaction scheme. The resulting alkyne can be reduced under conventional hydrogenation conditions to provide a compound of Formula IX, where R_{A2} is alkenyl or alkyl. Step (6) may also be carried out by (i) protecting the amino group of the compound of Formula XXXIV, for example, with a Boc group; (ii) performing a lithium-halogen exchange; (iii) treating with an electrophile of the Formula R_{A2}-Halide, for example iodomethane; and (iv) deprotecting the amine to provide a compound of Formula IX. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme VI



For some embodiments, compounds of the invention are prepared according to Reaction Scheme VII, wherein R, R_2, R_4, R_8, Q, M, and n are as defined above. In step (1) of Reaction Scheme VII, 4-phthalimido-2-butanone, which is obtained from the literature procedure, Eriks *et al*, *J. Med. Chem.*, *35*, 3239-3246, (1992), undergoes a Claisen condensation with diethyl oxalate under conventional conditions to yield a compound of Formula XXXV.

In step (2) of Reaction Scheme VII, a compound of Formula XXXV reacts with a hydrazine of Formula R_2NHNH_2 to provide a pyrazole carboxylate of Formula XXXVI. The reaction is conveniently carried out as described in Step (1) of Reaction Scheme I.

In steps (3) and (4) of Reaction Scheme VII, a pyrazole carboxylate of Formula XXXVI is converted to a pyrazole carboxamide. In step (3) the pyrazole carboxylate of Formula XXXVI is first hydrolyzed under acidic conditions to provide a carboxylic acid of Formula XXXVII. The reaction is conveniently carried out by heating a mixture of the carboxylate of Formula XXXVI in a mixture of hydrochloric acid and acetic acid at an elevated temperature, such as 100-120 °C. The product can be isolated by conventional methods. In step (4), a carboxylic acid of Formula XXXVII is then converted to its acid chloride. The reaction is conveniently carried out by heating (115 °C) the carboxylic acid of Formula XXXVII with thionyl chloride in a suitable solvent such as toluene. The acid chloride can be isolated by conventional methods before converting it to a pyrazole carboxamide of Formula XXXVIII. The conversion to the amide is conveniently carried out by adding concentrated ammonium hydroxide to a solution of the acid chloride in a suitable solvent such as dichloromethane. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

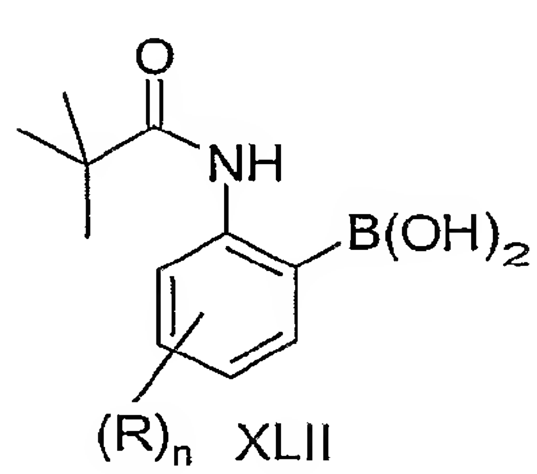
In step (5) of Reaction Scheme VII, a pyrazole carboxamide of Formula XXXVIII is dehydrated to a pyrazole carbonitrile of Formula XXXIX. Suitable dehydrating agents include thionyl chloride, trifluoroacetic anhydride, and phosphorous oxychloride. The reaction is conveniently carried out by treating a pyrazole carboxamide of Formula XXXVIII with excess thionyl chloride in a suitable solvent such as toluene. The reaction can be run at elevated temperture, for example, at the reflux temperature of the solvent, and the product can be isolated using conventional methods.

In step (6) of Reaction Scheme VII, a pyrazole carbonitrile of Formula XXXIX is brominated according to the method described in step (4) of Reaction Scheme I to provide a bromo-substituted pyrazole carbonitrile of Formula XL.

In step (7) of Reaction Scheme VII, the phthalimide protecting group of the pyrazole of Formula XL is removed to reveal an amine, which is then protected by a *tert*-butoxycarbonyl (Boc) group. The deprotection is conveniently carried out by treating the compound of Formula XL with hydrazine in a suitable solvent such as ethanol. The reaction can be run at an elevated temperature, such as the reflux temperature of the solvent, and the amine can be isolated using conventional methods. The Boc protection is then conveniently carried out by treating the amine with di-*tert*-butyl dicarbonate in a suitable solvent such as 1-methyl-2-pyrrolidinone (NMP). The reaction can be carried out at ambient temperature, and the product of Formula XLI can be isolated by conventional methods.

In steps (8) and (9a) of Reaction Scheme VII, a bromo-substituted pyrazole carbonitrile of Formula XLI undergoes a transition-metal catalyzed cross coupling reaction with a reagent of Formula XV to form a pyrazole-substituted aniline of Formula XLIII, which undergoes intramolecular cyclization and removal of the Boc group under acidic conditions in step (9a) to provide a pyrazolo[3,4-*c*]quinoline of Formula XLV, a subgenus of Formulas I, II, III, and Ia. Steps (8) and (9a) of Reaction Scheme VII can be carried out as described in steps (5) and (6) of Reaction Scheme I.

Alternatively, in step (8) of Reaction Scheme VII, a bromo-substituted pyrazole carbonitrile of Formula XLI undergoes a Suzuki coupling with a reagent of Formula XLII.



XLII

The resulting pivaloylamino-substituted compound undergoes a base-promoted intramolecular cyclization in step (9) of Reaction Scheme VII and subsequent cleavage of the pivaloyl group to provide a pyrazolo[3,4-*c*]quinoline of Formula XLIV, a subgenus of Formulas I, II, III, and Ia. The reaction with XLII and the base-promoted cyclization are

carried out as described in steps (5) and (6) of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (10) of Reaction Scheme VII, the Boc protecting group on a pyrazolo[3,4-*c*]quinoline of Formula XLIV is removed to provide an aminoethyl pyrazolo[3,4-*c*]quinoline of Formula XLV, a subgenus of Formulas I, II, III, and Ia. The deprotection is conveniently carried out under acidic conditions by adding hydrogen chloride in ethanol to a pyrazolo[3,4-*c*]quinoline of Formula XLIV in a suitable solvent such as ethanol. The reaction can be run at ambient temperature, and the product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

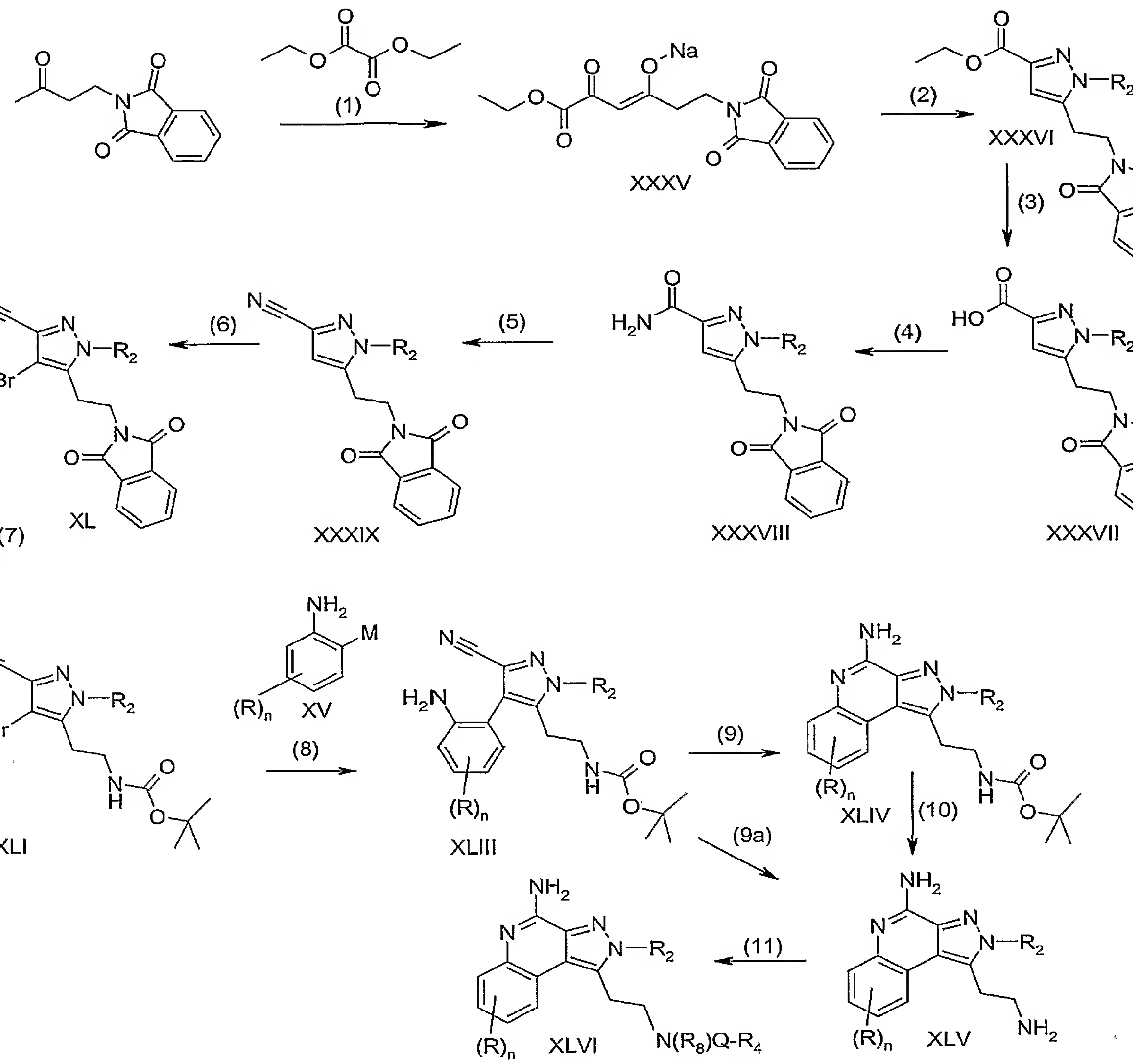
In step (11) of Reaction Scheme VII, an aminoethyl-2*H*-pyrazolo[3,4-*c*]quinoline of Formula XLV or pharmaceutically acceptable salt thereof is converted to an amide, sulfonamide, sulfamide, or urea of Formula XLVI using conventional methods. Formula XLVI represents a subgenus of Formula I, II, III, and Ia. In step (11), an aminoethyl-2*H*-pyrazolo[3,4-*c*]quinoline of Formula XLV can react with an acid chloride of Formula $R_4C(O)Cl$ to provide a compound of Formula XLVI in which -Q- is -C(O)-. In addition, an aminoethyl-2*H*-pyrazolo[3,4-*c*]quinoline of Formula XLV can react with sulfonyl chloride of Formula $R_4S(O)_2Cl$ or a sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to provide a compound of Formula XLVI in which -Q- is $-S(O)_2-$. Numerous acid chlorides of Formula $R_4C(O)Cl$, sulfonyl chlorides of Formula $R_4S(O)_2Cl$, and sulfonic anhydrides of Formula $(R_4S(O)_2)_2O$ are commercially available; others can be readily prepared using known synthetic methods. The reaction is conveniently carried out by adding the acid chloride of Formula $R_4C(O)Cl$, sulfonyl chloride of Formula $R_4S(O)_2Cl$, or sulfonic anhydride of Formula $(R_4S(O)_2)_2O$ to a solution of the aminoethyl-2*H*-pyrazolo[3,4-*c*]quinoline of Formula XLV in a suitable solvent such as chloroform, dichloromethane, or DMF. Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Ureas of Formula XLVI, where -Q- is $-C(O)-N(R_8)-$ and R_8 is as defined above, can be prepared by reacting an aminoethyl-2*H*-pyrazolo[3,4-*c*]quinoline of Formula XLV or pharmaceutically acceptable salt thereof with isocyanates of Formula $R_4N{=}C{=}O$ or with

carbamoyl chlorides of Formula R_4N-(R_8)-C(O)Cl. Numerous isocyanates of Formula R_4N=C=O and carbamoyl chlorides of Formula R_4N-(R_8)-C(O)Cl are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the isocyanate of Formula R_4N=C=O or carbamoyl chloride of Formula R_4N-(R_8)-C(O)Cl to a solution of the aminoethyl-2*H*-pyrazolo[3,4-*c*]quinoline of Formula XLV in a suitable solvent such as DMF or chloroform. Optionally a base such as triethylamine or *N,N*-diisopropylethylamine can be added. The reaction can be carried out at ambient temperature or a sub-ambient temperature such as 0 °C. Alternatively, a compound of Formula XLV can be treated with an isocyanate of Formula R_4(CO)N=C=O, a thioisocyanate of Formula R_4N=C=S, or a sulfonyl isocyanate of Formula $R_4S(O)_2N$=C=O to provide a compound of Formula XLVI, where -Q- is -C(O)-N(R_8)-(CO)-, -C(S)-N(R_8)-, or
-C(O)-N(R_8)-$S(O)_2$-, respectively. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Sulfamides of Formula XLVI, where -Q- is –$S(O)_2$-N(R_8)-, can be prepared by reacting a compound or salt of Formula XLV with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of formula HN(R_8)R_4. Alternatively, sulfamides of Formula XLVI can be prepared by reacting a compound of Formula XLV with a sulfamoyl chloride of formula R_4(R_8)N-$S(O)_2$Cl. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Many amines of Formula HN(R_8)R_4 and some sulfamoyl chlorides of formula R_4(R_8)N-$S(O)_2$Cl are commercially available; others can be prepared using known synthetic methods. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VII



For some embodiments, compounds of the invention are prepared according to Reaction Scheme VIII; wherein R, R_2, R_4, R_8, Q, M, Y, and n are as defined above; X_a is alkylene optionally interrupted with one or more -O- groups, wherein there are at least four atoms in the linking chain; and R_{4a} is heterocyclyl that is unsubstituted or substituted as defined in R_4 above, wherein the heterocyclyl is attached at a nitrogen atom. In step (1) of Reaction Scheme VIII, a chloro-substituted ketoester of Formula XLVII reacts with a hydrazine of Formula R_2NHNH_2 to provide a pyrazole carboxylate of Formula XLVIII. Compounds of Formula XLVII are readily prepared by reacting diethyl oxalate with ketones of Formula CH_3-C(O)-X_a-Cl under Claisen condensation conditions. Some

ketones of Formula CH_3-C(O)-X_a-Cl are commercially available; others can be prepared by known synthetic methods. The reaction in step (1) is conveniently carried out as described in step (1) of Reaction Scheme I.

In step (2) of Reaction Scheme VIII, a chloro-substituted pyrazole carboxylate of Formula XLVIII is converted to an acetate-substituted pyrazole carboxylate of Formula XLIX. The reaction is conveniently carried out by treating a chloro-substituted pyrazole carboxylate of Formula XLVIII with potassium acetate and sodium iodide in a suitable solvent such as DMF. The reaction can be carried out at an elevated temperature such as 90 °C, and the product can be isolated using conventional methods.

In step (3) of Reaction Scheme VIII, the ester group of a pyrazole carboxylate of Formula XLIX is converted to an amide according to the reaction conditions described in step (2) of Reaction Scheme I. Under the reaction conditions, the acetate group of the compound of Formula XLIX is converted to a hydroxyl group to provide a compound of Formula L, which can be isolated using conventional methods.

In step (4) of Reaction Scheme VIII, a pyrazole carboxamide of Formula L is dehydrated to a pyrazole carbonitrile according to the reaction conditions described in step (3) of Reaction Scheme I. Under these reaction conditions, the hydroxyl group of the compound of Formula L is converted to a chloro group to provide a compound of Formula LI, which can be isolated using conventional methods.

In steps (5) and (6) of Reaction Scheme VIII, a pyrazole carbonitrile of Formula LI is first brominated to provide a pyrazole carbonitrile of Formula LII, which then undergoes a transition-metal catalyzed cross coupling reaction to provide a pyrazole-substituted aniline of Formula LIII. Steps (5) and (6) of Reaction Scheme VIII are conveniently carried out as described in steps (4) and (5) of Reaction Scheme I.

In step (7) of Reaction Scheme VIII, the amine and nitrile functionalities of a pyrazole-substituted aniline of Formula LIII react under acidic conditions to form a pyrazolo[3,4-*c*]quinoline of Formula LIV, which is a subgenus of Formulas I, II, III, and Ia. The intramolecular addition is conveniently carried out by heating at reflux a pyrazole-substituted aniline of Formula LIII in the presence of hydrogen chloride in a suitable solvent such as ethanol. The reaction may also be carried out as described in step (6) of

Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

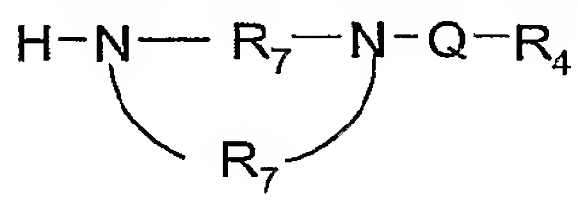
In step (8) or (8a) of Reaction Scheme VIII, a chloro-substituted pyrazolo[3,4-*c*]quinoline of Formula LIV reacts with a nucleophile to provide a pyrazolo[3,4-*c*]quinoline of Formula LV or LVa, subgenera of Formulas I, II, III, and Ia. For example, a compound of Formula LIV can react with methanesulfonamide to provide a compound of Formula LV, wherein -Y-R_4 is -NH-$S(O)_2$-CH_3. The reaction is conveniently carried out by combining sodium hydride and methanesulfonamide in a suitable solvent such as DMF and then adding a compound of Formula LIV and sodium iodide. The reaction can be carried out at an elevated temperature such as 80-90 °C. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Also, in step (8) of Reaction Scheme VIII, the chloro group on a pyrazolo[3,4-*c*]quinoline of Formula LIV can be displaced by a thiol under basic conditions to provide a compound of Formula LV where -Y- is -S-. The reaction is conveniently carried out by adding a thiol to a solution of a pyrazolo[3,4-*c*]quinoline of Formula LIV in the presence of a base such as potassium *tert*-butoxide in a suitable solvent such as DMF. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods. A compound of Formula LV where -Y- is -S- can then be oxidized to a compound of Formula LV where -Y- is -$S(O)_2$- using conventional oxidizing agents. The reaction is conveniently carried out by adding peracetic acid to the compound of Formula LV where -Y- is -S- in a suitable solvent. The conversion of a compound of Formula LIV to a compound of Formula LV where -Y- is -$S(O)_2$- can conveniently be carried out in one pot without isolating the thioether from the reaction mixture. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Alternatively, the chloro group of a pyrazolo[3,4-*c*]quinoline of Formula LIV can displaced with potassium thioacetate. The reaction is conveniently carried out at ambient temperature by adding potassium thioacetate to a solution of a pyrazolo[3,4-*c*]quinoline of Formula LIV in a suitable solvent such as DMF. The thioacetate group can then be cleaved under basic conditions at ambient temperature by adding a solution of sodium methoxide in methanol to provide a compound of Formula LV wherein -Y-R_4 is -SH. A thiol-substituted pyrazolo[3,4-*c*]quinoline of Formula LV can then be oxidized by

treatment with chlorine, prepared *in situ* from benzyltributylammonium chloride and trichloroisocyanuric acid, in a suitable solvent such as dichloromethane at 0 °C to provide a sulfonyl chloride, which is then treated with an amine hydrochloride of Formula $(R_4)(R_8)NH \bullet HCl$ followed by aqueous potassium carbonate in a suitable solvent such as dichloromethane to provide a compound of Formula LV wherein -Y- is $-S(O)_2-N(R_8)-$. The reaction with the amine hydrochloride can be carried out at ambient temperature, and the product can be isolated using conventional methods.

The chloro group on a pyrazolo[3,4-*c*]quinoline of Formula LIV can also be displaced by an amine of Formula



, several of which are commercially available. Other amines of this formula can be prepared by conventional methods. The reaction is conveniently carried out by combining a pyrazolo[3,4-*c*]quinoline of Formula LIV and the amine in the presence of a base such as potassium carbonate and in a suitable solvent such as DMF. Catalytic sodium iodide can optionally be added. The reaction can be carried out at an elevated temperature such as 50 °C or 90-100 °C, and the product can be isolated by conventional methods. These reaction conditions can also be used employing a variety of tertiary amines to provide compounds of Formula LV wherein Y is $-N(R_8)-$, a variety of phenols to provide compounds of Formula LV wherein Y is -O- and R_4 is an unsubstituted or substituted phenyl group, or employing a variety of commercially available cyclic amines in step (8a) to provide compounds of Formula LVa.

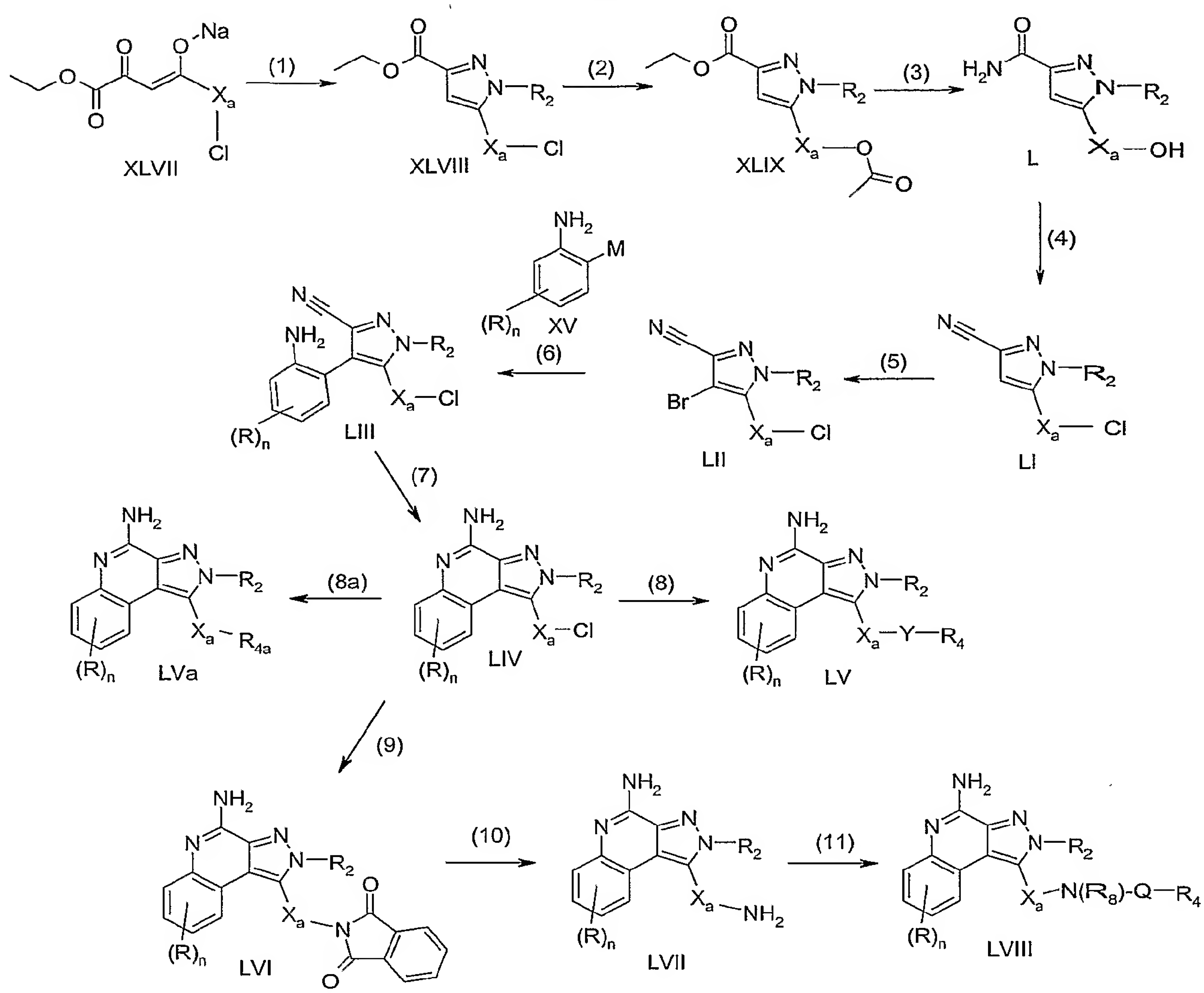
In step (9) of Reaction Scheme VIII, the chloro group of a pyrazolo[3,4-*c*]quinoline of Formula LIV is displaced by potassium phthalimide to provide a pyrazolo[3,4-*c*]quinoline of Formula LVI. The reaction is conveniently carried out by combining potassium phthalimide, sodium iodide, and a pyrazolo[3,4-*c*]quinoline of Formula LIV in a suitable solvent such as DMF and heating at an elevated temperature such as 90-100 °C. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (10) of Reaction Scheme VIII, the phthalimide protecting group of the pyrazolo[3,4-*c*]quinoline of Formula LVI is removed to reveal an amine of Formula LVII, a subgenus of Formula I, II, III, and Ia. The deprotection is conveniently carried out by

treating the compound of Formula LVI with hydrazine in a suitable solvent such as ethanol. The reaction can be run at an elevated temperature, such as the reflux temperature of the solvent, and the product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (11) of Reaction Scheme VIII, an aminoalkylpyrazolo[3,4-*c*]quinoline of Formula LVII or pharmaceutically acceptable salt thereof is converted to an amide, sulfonamide, sulfamide, or urea of Formula LVIII, which is a subgenus of Formulas I, II, III, and Ia. Step (11) of Reaction Scheme VIII can be carried out using the procedures described for step (11) of Reaction Scheme VII. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VIII



Compounds of the invention are also prepared by Reaction Scheme IX, wherein R_{2c} is $-R_4$, $-X_c-R_4$, and $-X_c-Y-R_4$; X_c is alkylene optionally terminated with arylene; and R, R_1, Y, R_4, and n are as defined above. In step (1) of Reaction Scheme IX, the benzyl group of a pyrazolo[3,4-*c*]quinoline of Formula LIX is cleaved to provide a pyrazolo[3,4-*c*]quinoline of Formula LX, which is a subgenus of Formulas I, II, III, and Ia. Benzyl pyrazolo[3,4-*c*]quinolines of Formula LIX are available from the reactions shown in Reaction Schemes I, III, VII, and VIII using benzylhydrazine dihydrochloride in steps (1), (1), (2), and (1), respectively. Step (1) is conveniently carried out by heating the benzyl pyrazolo[3,4-*c*]quinoline of Formula LIX in the presence of hydrogen bromide and a

suitable solvent such as acetic acid at an elevated temperature such as 150 °C. Alternatively, the reaction can be carried out under hydrogenolysis conditions by exposing the benzyl pyrazolo[3,4-*c*]quinoline of Formula LIX to hydrogen pressure in the presence of a catalyst such as palladium on carbon in a suitable solvent such as methanol. The reaction is conveniently carried out in a Parr vessel at ambient temperature or at an elevated temperature such as 50 °C. The product of Formula LX or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In addition to 2-benzyl pyrazolo[3,4-*c*]quinolines of Formula LIX, 2-*tert*-butyl pyrazolo[3,4-*c*]quinolines are also convenient starting materials for Reaction Scheme IX. The cleavage of a *tert*-butyl group is conveniently carried out with aqueous hydrochloric acid at an elevated temperature, such as 100 °C, and the product of Formula LX can be isolated by conventional methods.

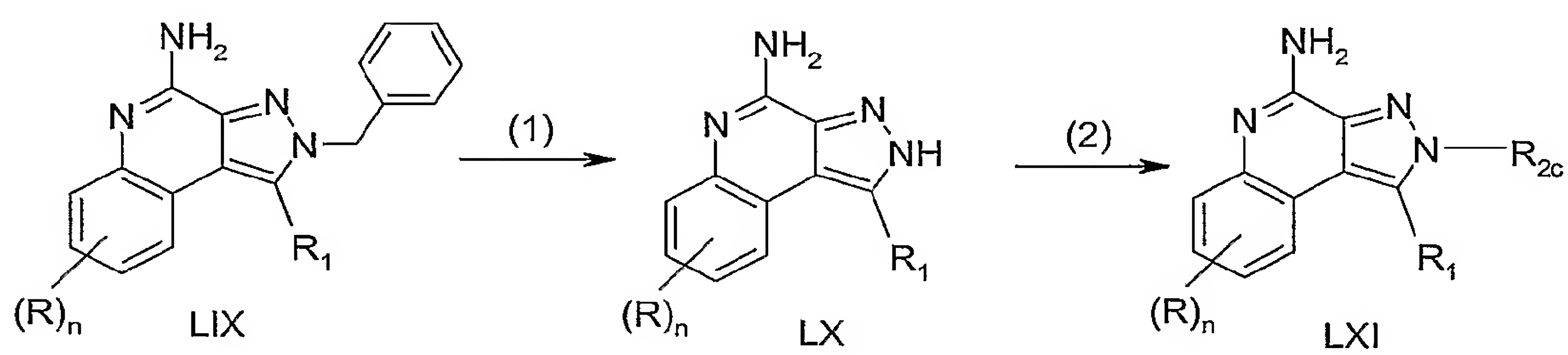
In step (2) of Reaction Scheme IX, a pyrazolo[3,4–*c*]quinoline of Formula LX is alkylated to provide a pyrazolo[3,4-*c*]quinoline of Formula LXI, a subgenus of Formulas I, II, III, and Ia. The reaction is conveniently carried out by adding an alkyl halide of Formula Halide-R_4, Halide-X_c-R_4, or Halide-X_c-Y-R_4 to a pyrazolo[3,4-*c*]quinoline of Formula LX in the presence of a base such as potassium carbonate in a suitable solvent such as DMF. The reaction can be run at ambient temperature. Several alkyl halides of the Formulas Halide-R_4, Halide-X_c-R_4, and Halide-X_c-Y-R_4 are commercially available, including many substituted alkyl iodides and bromides and substituted benzyl iodides and bromides. Other alkyl halides can be prepared by known synthetic methods. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Various functional groups can be introduced in step (2) of Reaction Scheme IX, and further synthetic elaboration is possible. For example, an alkyl halide of Formula Cl-alkylene-I can be used in step (2) to provide a compound of Formula LXI, wherein R_{2c} is a chloroalkylenyl group. The chloro group can then be displaced using one of a variety of methods described in steps (8) or (8a) of Reaction Scheme VIII. In another example, 4-bromobutylphthalimide can be used as the alkyl halide in step (2), and the resulting compound of Formula LXI bearing a phthalimide-protected amino group can be treated with hydrazine monohydrate to remove the phthalimide group. The deprotection is conveniently carried out in a suitable solvent such as ethanol at an elevated temperature,

such as the reflux temperature. The resulting aminoalkyl-substituted pyrazolo[3,4-*c*]quinoline of Formula LXI can then be treated according to step (11) of Reaction Scheme VII to provide a compound of Formula LXI wherein R_{2c} is -alkylene-N(R_8)-Q-R_4, and R_4, R_8, and Q are as defined above.

For some preferred embodiments, a compound of Formula LXI wherein R_{2c} is an ethoxy- or methoxyalkylenyl group is treated with boron tribromide to provide a compound of Formula LXI wherein R_{2c} is a hydroxyalkylenyl group. The reaction is conveniently carried out by adding a solution of boron tribromide to a compound of Formula LXI, wherein R_{2c} is an alkoxyalkylenyl group, in a suitable solvent such as dichloromethane. The reaction can be run at a sub-ambient temperature such as 0 °C, and the product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IX

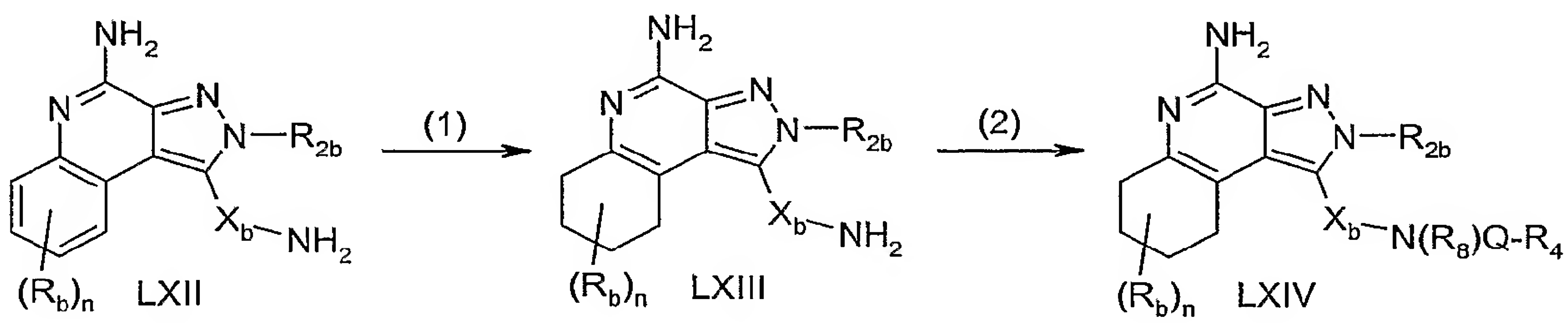


For some embodiments, tetrahydroquinolines of the invention can be prepared according to Reaction Scheme X, wherein R_b, R_{2b}, and n are as defined above and X_b is alkylene optionally interrupted or terminated by heterocyclylene and optionally interrupted by one or more -O- groups. Amino-substituted pyrazolo[3,4-*c*]quinolines of Formula LXII or pharmaceutically acceptable salts thereof can be prepared using any of the methods shown in Reaction Schemes I, VII, and VIII.

In step (1) of Reaction Scheme X, an amino-substituted pyrazolo[3,4-*c*]quinoline of Formula LXII is reduced to a tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXIII according to the method described in Reaction Scheme V. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (2) of Reaction Scheme X, an amino-substituted tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXIII is converted to an amide, sulfonamide, sulfamide, or urea of Formula LXIV, which is a subgenus of Formulas I, II, VIII, and Ia. Step (2) of Reaction Scheme X can be carried out using the procedures described for step (11) of Reaction Scheme VII. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme X



For some embodiments, compounds of the invention can be prepared according to Reaction Scheme XI, wherein n is as defined above; R_c is R for pyrazolo[3,4-*c*]quinolines or R_b for tetrahydropyrazolo[3,4-*c*]quinolines; R_{2d} is R_2 for pyrazolo[3,4-*c*]quinolines or R_{2b} for tetrahydropyrazolo[3,4-*c*]quinolines; R_{4s} is R_4 as defined above, with the proviso that the substituent on the alkyl, alkenyl, alkynyl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, or heterocyclyl group is not amino or alkylamino, or two R_{4s} groups in the same molecule can join to form a saturated ring or partially saturated ring system optionally containing one or more heteroatoms; X_d is alkylene optionally interrupted by one or more -O- groups, wherein there are at least three atoms in the linking chain; Boc is *tert*-butoxycarbonyl; and the bonds represented by dashed lines may be present or absent.

In step (1) of Reaction Scheme XI, the amino group of a pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LIVa is protected with two Boc groups to provide a compound of Formula LXV. Pyrazolo[3,4-*c*]quinolines of Formula LIVa can be prepared according to steps (1) through (7) of Reaction Scheme VIII. Tetrahydropyrazolo[3,4-*c*]quinolines of Formula LIVa can be prepared by reducing a pyrazolo[3,4-*c*]quinoline of Formula LIVa according to the method described in Reaction Scheme V. The protection reaction is conveniently carried out by combining a pyrazolo[3,4-*c*]quinoline or for tetrahydropyrazolo[3,4-*c*]quinoline of Formula LIVa with

di-*tert*-butyl dicarbonate in the presence of base, such as a combination of triethylamine and catalytic 4-dimethylaminopyridine (DMAP). The reaction can be carried out at ambient temperature in a suitable solvent such as toluene. The product can be isolated by conventional methods.

In step (2) of Reaction Scheme XI, a chloro-substituted compound of Formula LXV is converted to an acetate-substituted pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXVI according to the method described in step (2) of Reaction Scheme VIII.

In step (3) of Reaction Scheme XI, the acetate protecting group of a compound of Formula LXVI is removed to provide a hydroxy-substituted pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXVII. The reaction is conveniently carried out by combining a compound of Formula LXVI and potassium carbonate in a suitable solvent such as methanol at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) of Reaction Scheme XI, the alcohol of Formula LXVII is oxidized to an aldehyde-substituted pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXVIII using conventional methods, for example, Swern oxidation conditions. The Swern oxidation is conveniently carried out by adding a compound of Formula LXVII followed by triethylamine to a mixture of oxalyl chloride and dimethylsulfoxide in a suitable solvent, such as dichloromethane. The reaction can be carried out at sub-ambient temperatures, such as -78 °C, and the product can be isolated using conventional methods.

In step (5) of Reaction Scheme XI, an aldehyde-substituted compound of Formula LXVIII is converted to an alkenyl- or alkynyl-substituted compound of Formula LXIX. The conversion to an alkynyl-substituted compound is conveniently carried out by adding diethyl 1-diazo-2-oxopropylphosphonate to the aldehyde-substituted compound of Formula LXVIII in the presence of a mild base such as potassium carbonate. The reaction is carried out in a suitable solvent such as dichloromethane or methanol at ambient temperature. The aldehyde-substituted compound of Formula LXVIII can be converted to an alkenyl-substituted compound of Formula LXIX using synthetic methods well known to those skilled in the art; such methods include the Wittig reaction. The product can be isolated using conventional methods.

In step (6) of Reaction Scheme XI, the alkene or alkyne dipolarophile of Formula LXIX undergoes a cycloaddition reaction with a nitrone of Formula LXX or a nitrile oxide formed from an α-chloroaldoxime of Formula LXXI to provide a isoxazole, isoxazoline, or isoxazolidine-substituted pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXXII. Nitrones of Formula LXX are known and can be prepared by known methods. See, for example, Dicken, C. M. and DeShong, P., *J. Org. Chem.*, 47, pp. 2047-2051 (1982). Nitrones of Formula LXX wherein two vicinal R_{4s} groups join to form a saturated carbon ring can be prepared according to the literature procedures: Thesing, J.; Sirrenberg, W., *Chem. Ber.*, 92, p. 1748, (1959) and Iwashita, T. et al., *J. Org. Chem.*, 47, p. 230, (1982). The cycloaddition reaction shown in step (6) can be carried out by combining the nitrone of Formula LXX with a compound of Formula LXIX in a suitable solvent such as toluene and heating at an elevated temperature, for example, the reflux temperature of the solvent. Nitrones of Formula LXX can also be prepared in situ by combining a hydroxylamine of Formula R_{4s}-NH-OH or a hydrochloride salt thereof and an aldehyde or ketone of Formula $(R_{4s})_2C{=}O$ with a compound of Formula LXIX in the presence of a base such as sodium bicarbonate and alumina. The reaction can be carried out at an elevated temperature in a suitable solvent such as toluene. The product can be isolated using conventional methods.

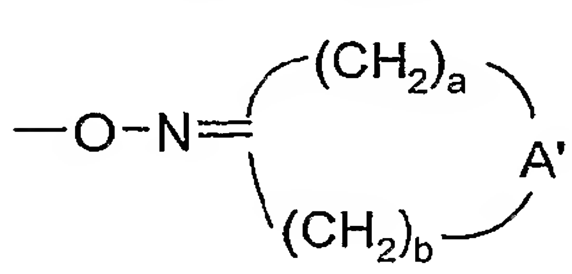
α-Chloroaldoximes of Formula LXXI can be prepared by treating an aldoxime of Formula $R_{4s}(H)C{=}N{-}OH$ with *N*-chlorosuccinimide at ambient temperature or at a sub-ambient temperature such as 0 °C in a suitable solvent such as DMF or THF. The resulting α-chloroaldoxime of Formula LXXI is combined with a compound of Formula LXIX in the presence of a base such as triethylamine to generate a nitrile oxide in situ and effect the cycloaddition reaction. The reaction can be carried out at ambient temperature in a suitable solvent such as dichloromethane or THF. The product can be isolated using conventional methods. When an alkynyl-substituted compound of Formula LXIX is combined with an α-chloroaldoxime of Formula LXXI under these conditions, the product is an isoxazole of Formula LXXII.

In step (7) of Reaction Scheme XI, the Boc protecting groups are removed from a pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXXII according to the method described in step (10) of Reaction Scheme VII. The reaction may

be run at ambient temperature or at an elevated temperature such as 60 °C, and the product of Formula LXXIII or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

The Boc groups can be removed from other compounds shown in Reaction Scheme XI to provide pyrazolo[3,4-*c*]quinolines or tetrahydropyrazolo[3,4-*c*]quinolines of the invention. For example, the conditions described in step (7) can be used to treat compounds of Formula LXVII, LXVIII, or LXIX to reveal pyrazolo[3,4-*c*]quinolin-4-amines or tetrahydropyrazolo[3,4-*c*]quinolin-4-amines with a hydroxy, aldehyde, alkene, or alkyne group at R_1.

Some compounds shown in Reaction Scheme XI are useful starting materials for the preparation of other compounds of the invention. For example, a hydroxyalkyl-substituted pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXVII can be treated with *N*-hydroxyphthalimide under Mitsunobu reaction conditions to provide an *N*-phthalimide-protected hydroxylamine. The reaction is conveniently carried out by adding triphenylphosphine and *N*-hydroxyphthalimide to a solution of the alcohol of Formula LXVII in a suitable solvent such as tetrahydrofuran or DMF and then slowly adding diisopropyl azodicarboxylate. The reaction can be carried out at ambient temperature or at an elevated temperature, such as 60 °C. The phthalimide group can then be removed from the resulting *N*-phthalimide-protected hydroxylamine by treatment with hydrazine at ambient temperature in a suitable solvent such as ethanol. The resulting hydroxylamine can then be treated with one of numerous commercially available aldehydes or ketones in a suitable solvent such as methanol to provide an oxime. The Boc protecting groups of the resulting compound can then be removed as described in step (7) of Reaction Scheme XI to provide a compound of the invention, wherein R_1 is -X-Y-R_4 or -X-R_5, where X is X_d, which is defined above, Y is
-O-N=C(R_4)-, R_5 is

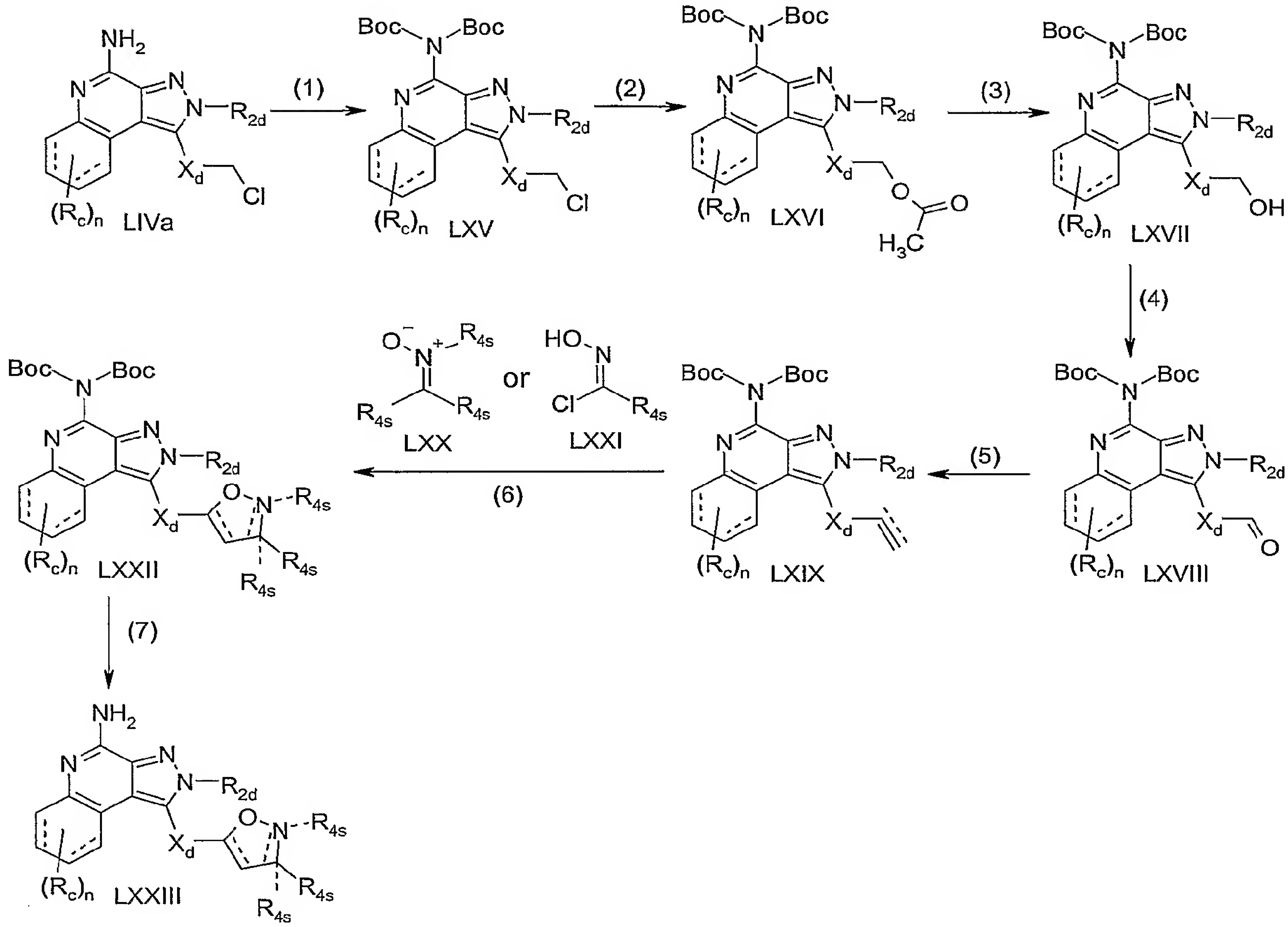


, and R_4 a, b, and A' are as defined above. Alternatively, the hydroxylamine prepared after the hydrazine deprotection may be treated with one of numerous acid chlorides, sulfonyl chlorides, isocyanates, carbamoyl chlorides, or sulfamoyl chlorides as described in step (11) of Reaction Scheme VII to provide, after

removal of the Boc protecting groups, a compound of the invention wherein R_1 is -X-Y-R_4 where X is X_d, Y is -O-NH-Q-, and Q and R_4 are as defined above.

In another example, an aldehyde-substituted pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXVIII can optionally be treated with a Grignard reagent of Formula R_4-Mg-X under conventional Grignard conditions to provide a secondary alcohol. It may be necessary to remove the Boc groups prior to this reaction and install different amine protecting groups known to one skilled in the art to be less reactive toward Grignard reagents. The secondary alcohol can then be oxidized under Swern conditions as described in step (4) of Reaction Scheme XI, and the protecting groups may subsequently be removed to provide a ketone, which is a compound of the invention wherein R_1 is -X-Y-R_4 where X is X_d, Y is -C(O)-, and R_4 is as defined above. The ketone can then be converted to an oxime by adding an aqueous solution of a hydroxylamine salt of Formula NH_2OR_8•HCl to a solution of the ketone in a suitable solvent such as methanol or ethanol and then adding a base such as sodium hydroxide and heating at an elevated temperature to provide a compound of the invention, wherein R_1 is -X-Y-R_4 where X is X_d, Y is -C(=N-OR_8)-, and R_4 and R_8 are as defined above. The oxime so prepared may be reduced with sodium cyanoborohydride in a mixture of ethanol or methanol in acetic acid to provide a hydroxylamine, which may be treated with one of numerous acid chlorides, sulfonyl chlorides, isocyanates, carbamoyl chlorides, or sulfamoyl chlorides as described in step (11) of Reaction Scheme VII to provide a compound of the invention wherein R_1 is -X-Y-R_4 where X is X_d, Y is -CH(-N-(OR_8)-Q-R_4)-, and Q, R_4, and R_8 are as defined above.

Reaction Scheme XI



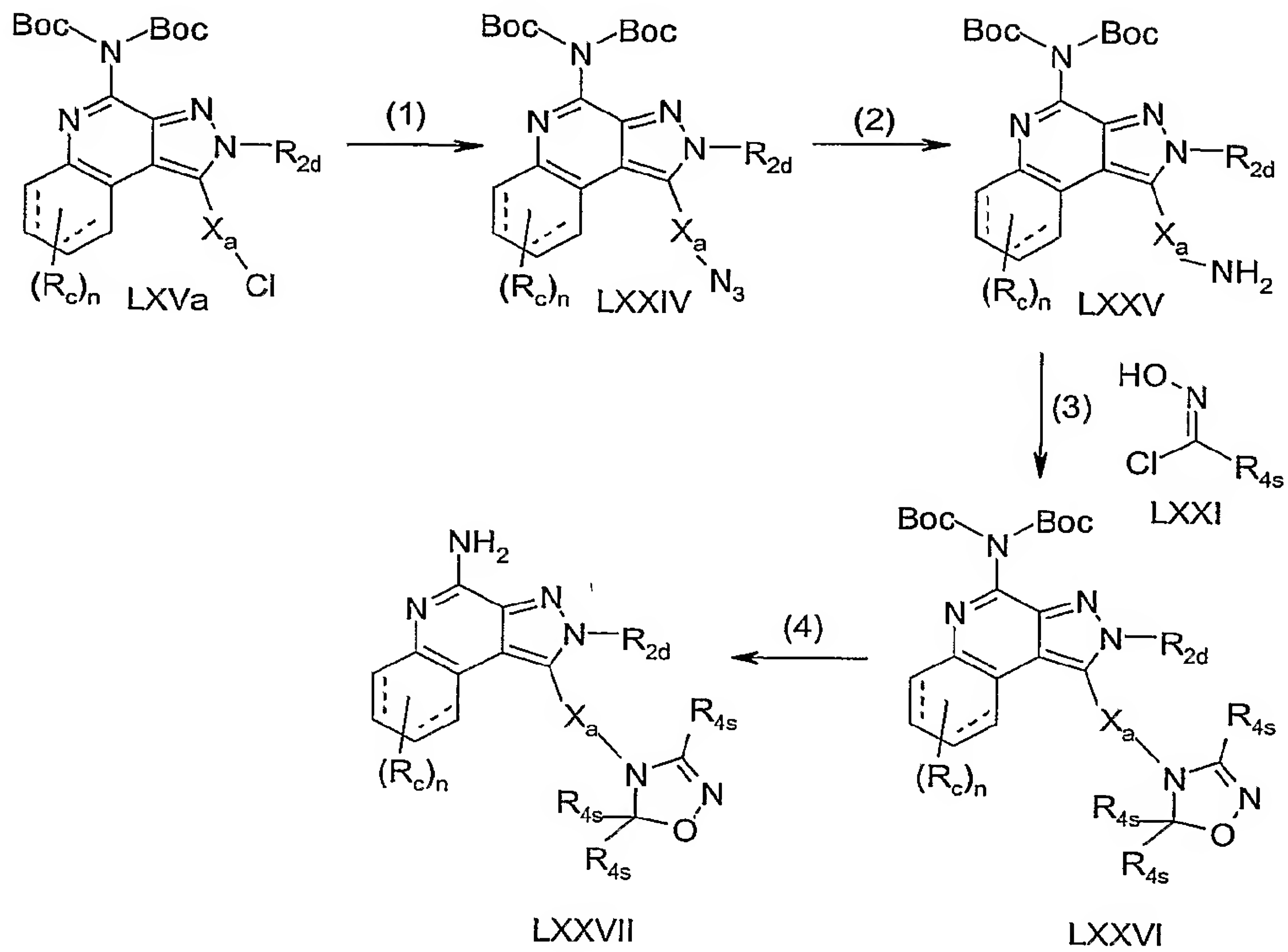
Compounds of the invention can also be prepared according to Reaction Scheme XII, wherein R_c, R_{2d}, Boc, R_{4s}, X_a, and n are as defined above, and the bonds represented by dashed lines may be present or absent. In steps (1) and (2) of Reaction Scheme XII, a 1-chloroalkyl-substituted pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXVa, prepared according to the method described in step (1) of Reaction Scheme XI, is converted to a 1-aminoalkyl-substituted compound of Formula LXXV. Step (1) is conveniently carried out by adding sodium azide and sodium iodide to a 1-chloroalkyl-substituted compound of Formula LXVa in a suitable solvent such as DMF. The reaction can be carried out at an elevated temperature such as 90 °C, and the azide of Formula LXXIV can be isolated by conventional methods prior to reduction in step (2). Step (2) is conveniently carried out by adding triphenylphosphine to an azide-substituted pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXXIV in a

suitable solvent or solvent mixture such as tetrahydrofuran/water. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods. Aminoalkyl-substituted pyrazolo[3,4-*c*]quinolines or tetrahydropyrazolo[3,4-*c*]quinolines of Formula LXXV may also be prepared using methods shown in Reaction Scheme VIII.

In step (3) of Reaction Scheme XII, an aminoalkyl-substituted pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXXV is converted to an imine by reaction with a ketone or aldehyde of Formula $(R_{4s})_2C{=}O$ and subsequently treated with an α-chloroaldoxime of Formula LXXI. The reaction is conveniently carried out by combining an aminoalkyl-substituted compound of Formula LXXV with a ketone or aldehyde of Formula $(R_{4s})_2C{=}O$ at ambient temperature in a suitable solvent such as dichloromethane. The reaction can optionally be carried out in the presence of magnesium sulfate. The resulting imine is then combined with an α-chloroaldoxime of Formula LXXI according to the procedure described in step (6) of Reaction Scheme XI. The product of Formula LXXVI can be isolated using conventional methods.

In step (4) of Reaction Scheme XII, the Boc protecting groups are removed from a pyrazolo[3,4-*c*]quinoline or tetrahydropyrazolo[3,4-*c*]quinoline of Formula LXXVI according to the method described in step (7) of Reaction Scheme XI. The product of Formula LXXVII or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme XII



For some embodiments, compounds of the invention are prepared according to Reaction Scheme XIII, wherein R_1, R_2, and n are defined as above; R is selected from the group consisting of halogen, alkyl, alkenyl, trifluoromethyl, and dialkylamino; and R_{3a} and R_{3b} are defined below. In step (1) of Reaction Scheme XIII, a bromo-substituted pyrazole carbonitrile of Formula XIV undergoes a transition-metal catalyzed cross coupling reaction with a reagent of Formula XLIIa. Some compounds of Formula XLIIa are known; see, Adams, L., *J. Heterocyclic Chem.*, 32, p. 1171 (1995). Others can be prepared by known synthetic methods; see, Rocca, P. *et al*, *Tetrahedron*, 49, pp. 49-64 (1993). The Suzuki coupling reaction can be carried out as described in step (5) of Reaction Scheme I to provide a

compound of Formula LXXVIII, and the product can be isolated by conventional methods.

In step (2) of Reaction Scheme XIII, a pivaloylamino-substituted compound of Formula LXXVIII undergoes a base-promoted intramolecular cyclization and subsequent cleavage of the pivaloyl group to provide a pyrazolo[3,4-*c*]quinoline of Formula XVIIa. The reaction can be carried out as described in Reaction Scheme I, and the product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (3) of Reaction Scheme XIII, the methoxy group of a pyrazolo[3,4-*c*]quinoline of Formula XVIIa is demethylated to provide a hydroxy-substituted pyrazolo[3,4-*c*]quinoline of Formula XVIIb. The demethylation is conveniently carried out by treating the compound of Formula XVIIa with a solution of boron tribromide in a suitable solvent such as dichloromethane. The reaction can be carried out at a sub-ambient temperature such as 0 °C, and the product or pharmaceutically acceptable salt thereof can be isolated using conventional methods. Alternatively, the demethylation is carried out by heating the compound of Formula XVIIa with anhydrous pyridinium chloride at an elevated temperature, such as 210 °C. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) of Reaction Scheme XIII, the hydroxy group of a pyrazolo[3,4-*c*]quinoline of Formula XVIIb is activated by conversion to a trifluromethanesulfonate (triflate) group. The reaction is conveniently carried out by treating a hydroxy-substituted pyrazolo[3,4-*c*]quinoline of Formula XVIIb with *N*-phenyl-bis(trifluoromethanesulfonimide) in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature in a suitable solvent such as DMF, and the triflate of Formula LXXX can be isolated using conventional methods. The activation in step (4) may also be accomplished by converting the hydroxy group to another good leaving group.

Step (5) of Reaction Scheme XIII can be carried out using known palladium-catalyzed coupling reactions such as the Suzuki coupling, Heck reaction, the Stille coupling, and the Sonogashira coupling. For example, a triflate-substituted pyrazolo[3,4-*c*]quinoline of Formula LXXX undergoes Suzuki coupling with a boronic acid of Formula R_{3a}-B(OH)$_2$, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-B(O-alkyl)$_2$; wherein R_{3a} is -R_{4b}, -X_e-R_4, -X_f-Y-R_4, or -X_f-R_5; where X_e is alkenylene; X_f is arylene, heteroarylene, and alkenylene interrupted or terminated by arylene or heteroarylene; R_{4b} is aryl or heteroaryl where the aryl or heteroaryl groups can be unsubstituted or substituted as defined in R_4 above; and R_4, R_5, and Y are as defined above. The coupling is carried out by combining a compound of Formula LXXX with a boronic acid or an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine, and a base such as aqueous sodium carbonate in a suitable solvent such as *n*-propanol. The reaction can be

carried out at an elevated temperature, for example, at the reflux temperature. Numerous boronic acids of Formula R_{3a}-$B(OH)_2$, anhydrides thereof, and boronic acid esters of Formula R_{3a}-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods. The product of Formula XVIIc or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Alternatively, the Heck reaction can be used in step (5) of Reaction Scheme XIII to provide compounds of Formula XVIIc, wherein R_{3a} is -X_e-R_{4b} or -X_e-Y-R_4, wherein X_e, Y, R_4, and R_{4b} are as defined above. The Heck reaction is carried out by coupling a compound of Formula LXXX with a compound of the Formula H_2C=C(H)-R_{4b} or H_2C=C(H)-Y-R_4. Several of these vinyl-substituted compounds are commercially available; others can be prepared by known methods. The reaction is conveniently carried out by combining the compound of Formula LXXX and the vinyl-substituted compound in the presence of palladium (II) acetate, triphenylphosphine or tri-*ortho*-tolylphosphine, and a base such as triethylamine in a suitable solvent such as acetonitrile or toluene. The reaction can be carried out at an elevated temperature such as 100-120 °C under an inert atmosphere. The product of Formula XVIIc or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of Formula XVIIc, wherein R_{3a} is -X_g-R_4, X_g is alkynylene, and R_4 is as defined above, can also be prepared by palladium catalyzed coupling reactions such as the Stille coupling or Sonogashira coupling. These reactions are carried out by coupling a compound of Formula LXXX with a compound of the Formula (alkyl)$_3$Sn-C≡C-R_4, (alkyl)$_3$Si-C≡C-R_4, or H-C≡C-R_4.

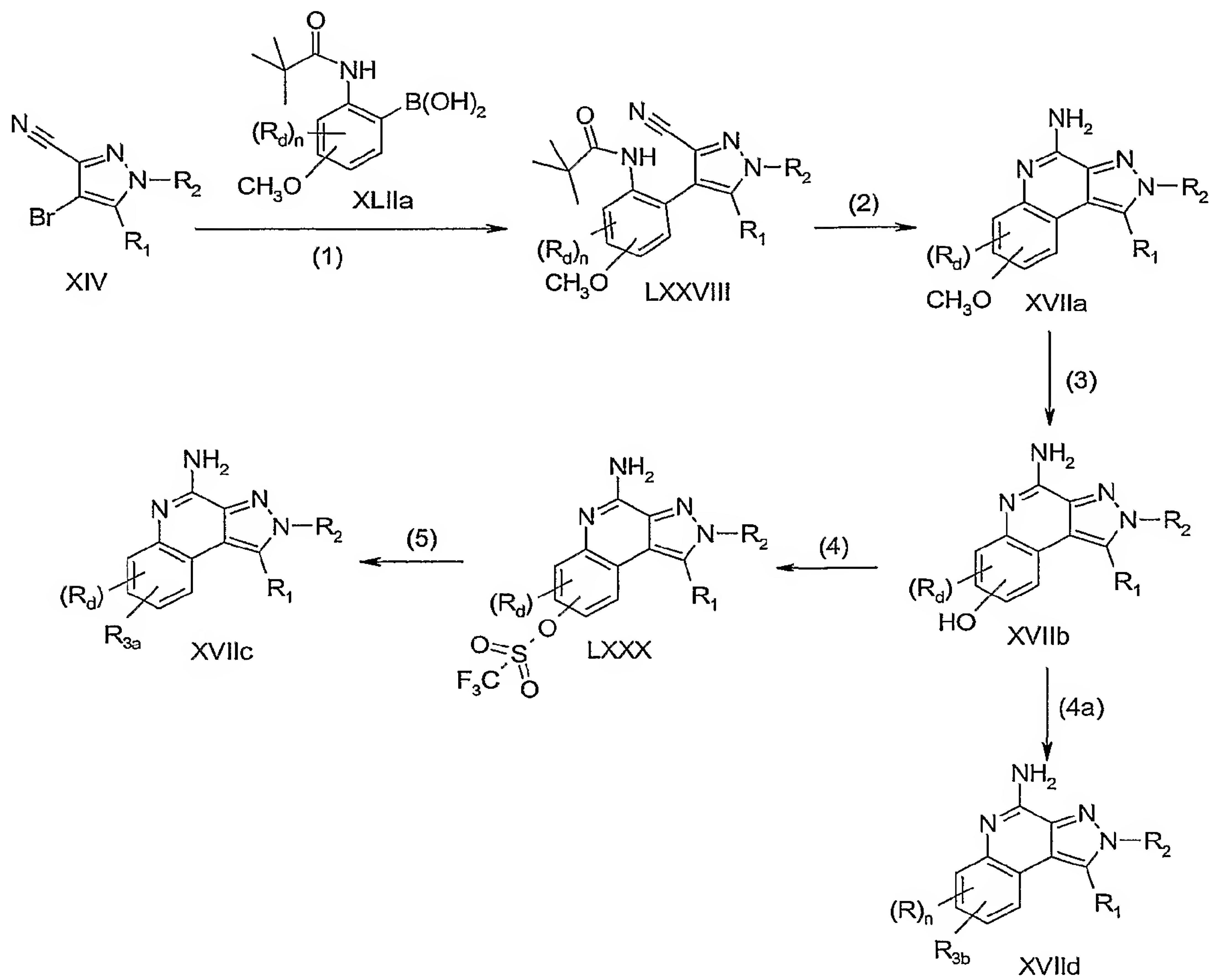
Compounds of Formula XVIIc prepared as described above by palladium-mediated coupling reactions, wherein R_{3a} is –X_e-R_4, -X_e-Y-R_4, -X_{f2}-Y-R_4, -X_{f2}-R_5, or –X_g-R_4, where X_{f2} is alkenylene interrupted or terminated by arylene or heteroarylene, and X_e, X_g, Y, R_4, and R_5 are as defined above, can undergo reduction of the alkenylene or alkynylene group present to provide compounds of Formula XVIIc wherein R_{3a} is –X_h-R_4, -X_h-Y-R_4, -X_i-Y-R_4, or –X_i-R_5, where X_h is alkylene; X_i is alkylene interrupted or terminated by arylene or heteroarylene; and R_4, R_5, and Y are as defined above. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr

apparatus in a suitable solvent such as ethanol, methanol, or mixtures thereof. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (4a) of Reaction Scheme XIII, a hydroxy-substituted pyrazolo[3,4-*c*]quinoline of Formula XVIIb is converted to a compound of Formula XVIId, wherein R_{3b} is -O-R_4, -O-X-R_4, -O-X-Y-R_4, or -O-X-R_5, and X, Y, R_4, and R_5 are as defined above, using a Williamson-type ether synthesis. The reaction is effected by treating a hydroxy-substituted pyrazolo[3,4-*c*]quinoline of Formula XVIIb with an aryl, alkyl, or arylalkylenyl halide of Formula Halide-R_4, Halide-alkylene-R_4, Halide-alkylene-Y-R_4, or Halide-alkylene-R_5 in the presence of a base. Numerous alkyl, arylalkylenyl, and aryl halides of these formulas are commercially available, including substituted benzyl bromides and chlorides, substituted or unsubstituted alkyl or arylalkylenyl bromides and chlorides, bromo-substituted ketones, esters, and heterocycles, and substituted fluorobenzenes. Other halides of these formulas can be prepared using conventional synthetic methods. The reaction is conveniently carried out by combining an alkyl, arylalkylenyl, or aryl halide with the hydroxy-substituted compound of Formula XVIIb in a solvent such as DMF or *N,N*-dimethylacetamide in the presence of a suitable base such as cesium carbonate. Optionally, catalytic tetrabutylammonium bromide can be added. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 50 °C or 85 °C, depending on the reactivity of the halide reagent.

Alternatively, step (4a) may be carried out using the Ullmann ether synthesis, in which an alkali metal aryloxide prepared from the hydroxy-substituted compound of Formula XVIIb reacts with an aryl halide in the presence of copper salts, to provide a compound of Formula XVIId, where R_{3b} is -O-R_{4b}, -O-X_j-R_4, or -O-X_j-Y-R_4, wherein X_j is an arylene or heteroarylene and R_{4b} is as defined above. Numerous substituted and unsubstituted aryl halides are commercially available; others can be prepared using conventional methods. The product of Formula XVIId, prepared by either of these methods, or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme XIII



Compounds of the invention can also be prepared using variations of the synthetic routes shown in Reaction Schemes I through XIII that would be apparent to one of skill in the art. For example, the synthetic routes shown in Reaction Schemes VII or VIII for the preparation of quinolines can be used to prepare naphthyridines by using a compound of Formula XVIII or a position isomer thereof in lieu of a compound of Formula XV. Compounds of the invention can also be prepared using the synthetic routes described in the EXAMPLES below.

Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce or inhibit the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising

administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Other cytokines whose production may be inhibited by the administration of compounds or salts of the invention include tumor necrosis factor-α (TNF-α). Among other effects, inhibition of TNF-α production can provide prophylaxis or therapeutic treatment of TNF-α mediated diseases in animals, making the compounds or salt useful in the treatment of, for example, autoimmune diseases. Accordingly, the invention provides a method of inhibiting TNF-α biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for inhibition of TNF-α biosynthesis may have a disease as described *infra*, for example an autoimmune disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogeous leukemia, chronic

lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, an IRM compound or salt of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Certain IRM compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, certain compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce or inhibit cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) or decreased (inhibited) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

Chromatographic purification was carried out by flash chromatography on either a HORIZON HPFC system (an automated, modular high-performance flash purification

product available from Biotage, Inc, Charlottesville, Virginia, USA) or an Analogix INTELLIFLASH Flash Chromatography System (IFC). The eluent used for each purification is given in the example. In some chromatographic separations, the solvent mixture 80:18:2 chloroform/methanol/concentrated ammonium hydroxide (CMA) was used as the polar component of the eluent. In these separations, CMA was mixed with chloroform in the indicated ratio. For Examples 1 through 6, chromatographic purification was carried out on a HORIZON HPFC system using either a FLASH 40+M cartridge, a FLASH 25+M, or a FLASH 65I Silica cartridge.

Examples 1-4

Part A

Ethyl 6-methyl-2,4-dioxoheptanoate, sodium salt is available from the literature procedure (Claisen, L., *Berichte*, 1909, *42*, 59) or can be prepared by the following method. A solution of diethyl oxalate (1 equivalent) and 3-methyl-2-butanone (1 equivalent) was added dropwise with vigorous stirring to a solution of sodium *tert*-butoxide (1 equivalent) in ethanol. Following the addition, the reaction was stirred for one hour; a precipitate formed. The precipitate was isolated by filtration, washed with ethanol and diethyl ether, and dried to provide ethyl 6-methyl-2,4-dioxoheptanoate, sodium salt.

Part B

Anhydrous hydrazine (3.58 g, 112 mmol) was added dropwise over a period of 30 minutes to a solution of ethyl 6-methyl-2,4-dioxoheptanoate, sodium salt (24.8 g, 112 mmol) in acetic acid (160 mL). The reaction was stirred overnight at ambient temperature, and then the solvent was removed under reduced pressure. The residue was dissolved in a mixture of diethyl ether and water, and solid sodium bicarbonate and sodium carbonate were added to adjust the mixture to pH 8. The aqueous layer was extracted twice with diethyl ether; the combined organic fractions were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on a HORIZON HPFC system (FLASH 65I cartridge, eluting with 50:50 ethyl acetate/hexanes) to provide 21.0 g of ethyl 5-(2-methylpropyl)-1*H*-pyrazole-3-carboxylate as a solid.

Part C

The alkylating agent from the table below (1.5 equivalents) and a solution of sodium ethoxide in ethanol (21%, 1.1 equivalents) were added to a solution of ethyl 5-(2-methylpropyl)-1*H*-pyrazole-3-carboxylate (1 equivalent) in ethanol (1M), and the reaction was heated at reflux under a nitrogen atmosphere for 90 minutes to two hours. An analysis by high-performance liquid chromatography (HPLC) indicated the presence of starting material. Additional sodium ethoxide solution (0.1-0.3 equivalents) was added, and the reaction was heated at reflux for an additional 30 minutes to two hours. For example 3, the reaction was stirred at ambient temperature overnight instead of heating at reflux. The solvent was removed under reduced pressure, and the residue was partitioned between aqueous sodium chloride and diethyl ether. The aqueous layer was extracted twice with diethyl ether, and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on a HORIZON HPFC system (FLASH 65I cartridge, eluting with hexane/ethyl acetate ranging in ratios from 80:20 to 50:50) to provide the alkylated pyrazole as a yellow oil.

Part D

Excess 30% ammonium hydroxide was added to a Parr vessel containing the material from Part C and methanol (1-2 M). The vessel was sealed, and the reaction was heated at 100 °C for 12 hours, allowed to cool to ambient temperature over a period of three hours, and then cooled to 0 °C. A solid formed and was isolated by filtration, washed with water and hexanes, and air-dried to provide the carboxamides listed below.

Example 1: 5-(2-Methylpropyl)-1-propyl-1*H*-pyrazole-3-carboxamide was obtained as white crystals, mp 141-142.5 °C.

Anal. Calcd. for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 62.93; H, 8.89; N, 20.01.

Example 2: 1-Ethyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carboxamide was obtained as white crystals, mp 125-126 °C.

Anal. Calcd. for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.50; H, 8.86; N, 21.58.

Example 3: At the completion of the reaction, the solvent was removed under reduced pressure. The residue was purified by chromatography on a HORIZON HPFC system (FLASH 65I cartridge, eluting with ethyl acetate/methanol ranging in ratios from 97:3 to 95:5) and subsequently recrystallized from *tert*-butyl methyl ether to provide 1-methyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carboxamide as white crystals, mp 118.5-119.5 °C.
Anal. Calcd. for $C_9H_{15}N_3O$: C, 59.65; H, 8.34; N, 23.18. Found: C, 59.66; H, 8.66; N, 23.25.

Example 4: At the completion of the reaction, water was added to precipitate the product, 1-butyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carboxamide, which was isolated as white crystals, mp 122.5-124 °C.
Anal. Calcd. for $C_{12}H_{21}N_3O$: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.65; H, 9.52; N, 18.77.

Part E

A mixture of the carboxamide from Part D (5-10 g, 28-45 mmol) and phosphorous oxychloride (21-38 mL) was heated at 90 °C for 90 minutes. The solution was then poured into ice water (250-500 mL), and concentrated ammonium hydroxide was added to adjust the mixture to pH 7-8. The mixture was extracted with dichloromethane (4 x), and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide an oil.

Part F

Potassium acetate (1.5 equivalents) and bromine (1.1 equivalents) were added to a solution of the carbonitrile from Part E in acetic acid (0.6 M), and the reaction was stirred for 15-24 hours. Saturated aqueous sodium hydrogensulfite (1 mL) was added, and the mixture was stirred until it became colorless. The acetic acid was removed under reduced pressure, and 2M aqueous sodium carbonate was added to the residue. The resulting solution was extracted with dichloromethane (4 x). The combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was purified by chromatography on a HORIZON HPFC system (FLASH 65I cartridge, eluting with hexane/ethyl acetate ranging in ratios from 98:2 to 65:35) to provide an oil.
In Example 2, 4-bromo-1-ethyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile crystallized under vacuum and was obtained as a white solid, mp 50-51 °C.

Anal. Calcd. for $C_{10}H_{14}N_3Br$: C, 46.89; H, 5.51; N, 16.40. Found: C, 46.95; H, 5.64; N, 16.75.

Part G

Triphenylphosphine (24 mg, 0.09 mmol) and palladium (II) acetate (7 mg, 0.03 mmol) were added to a mixture of the carbonitrile from Part F (10.0 mmol), 2-aminophenylboronic acid (12.0 mmol, Examples 2 and 3) or 2-aminophenylboronic acid hydrochloride (12.0 mmol, Examples 1 and 4), aqueous sodium carbonate (6 mL of 2 M, Examples 2 and 3 or 12 mL of 2M, Examples 1 and 4), propanol (17.5 mL) and water (3.5 mL). The reaction was heated under a nitrogen atmosphere at 100 °C for 12 to 33 hours; in Examples 3 and 4 additional triphenylphosphine, palladium (II) acetate, and boronic acid were added to drive the reaction to completion. The reaction mixture was allowed to cool to ambient temperature and then partitioned between water and chloroform. The aqueous layer was extracted with chloroform (3 x). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

The residue from Example 2 was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with dichloromethane/ethyl acetate ranging in ratios from 100:0 to 85:15). The residue from Example 3 was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with chloroform/CMA ranging in ratios from 99:1 to 95:5).

Part H

A solution of acetyl chloride (1.5 equivalents) in ethanol (0.3 M) was stirred for 15 minutes and added to the material from Part G, and the reaction was heated at reflux under a nitrogen atmosphere for 3.5 to 14 hours. The solvent was removed under reduced pressure, and the residue was partitioned between chloroform and 2 M aqueous sodium carbonate. The aqueous layer was extracted twice with chloroform, and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with chloroform/CMA ranging in ratios from 100:0 to 75:25) and subsequently recrystallized from acetonitrile. The crystals were dried overnight at 6.65 Pa and 98 °C to provide the products listed below.

Example 1: 1-(2-Methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was obtained as white needles, mp 199-200 °C.

Anal. Calcd. for $C_{17}H_{22}N_4$: C, 72.31; H, 7.85; N, 19.84. Found: C, 72.13; H, 8.03; N, 19.78.

Example 2: 2-Ethyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was obtained as white needles, mp 208-209 °C.

Anal. Calcd. for $C_{16}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.38; H, 7.83; N, 20.79.

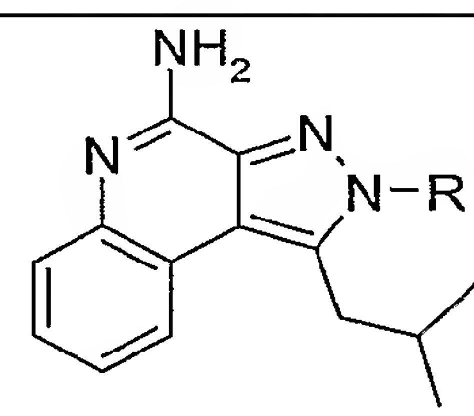
Example 3: 2-Methyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was obtained as light pink crystals, mp 213-214 °C.

Anal. Calcd. for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.59; H, 7.19; N, 22.05.

Example 4: 2-Butyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was obtained as white needles, mp 165-166 °C.

Anal. Calcd. for $C_{18}H_{24}N_4$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.89; H, 7.99; N, 19.08.

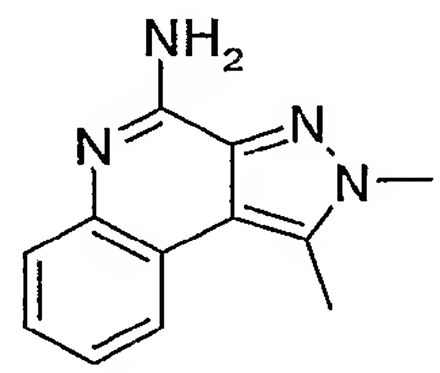
Examples 1-4



Example	Alkylating agent in Part C	R
1	1-Iodopropane	$-CH_2CH_2CH_3$
2	1-Bromoethane	$-CH_2CH_3$
3	Iodomethane	$-CH_3$
4	1-Iodobutane	$-CH_2CH_2CH_2CH_3$

Example 5

1,2-Dimethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine hydrochloride



Part A

Ethyl 1,5-dimethyl-1*H*-pyrazole-3-carboxylate is available from the literature procedure (Huppatz, J. L., *Aust. J. Chem.*, 1983, *36*, 135-147). The general method described in Part D of Examples 1 through 4 was used to convert ethyl 1,5-dimethyl-1*H*-pyrazole-3-carboxylate to 1,5-dimethyl-1*H*-pyrazole-3-carboxamide.

Part B

The method described in Part E of Examples 1 through 4 was used to treat 1,5-dimethyl-1*H*-pyrazole-3-carboxamide (5.0 g, 36 mmol) with phosphorous oxychloride (20 mL) to afford 3.9 g of 1,5-dimethyl-1*H*-pyrazole-3-carbonitrile. A small portion was recrystallized from hexane to provide the following data.

Anal. Calcd. for $C_6H_7N_3$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.31; H, 5.75; N, 34.48.

Part C

A solution of bromine (5.1 g, 32 mmol) in acetic acid (10 mL) was added dropwise to a solution of potassium acetate (3.9 g, 40 mmol) and 1,5-dimethyl-1*H*-pyrazole-3-carbonitrile in acetic acid (50 mL). Following the addition, the reaction was stirred for 30 minutes. Saturated aqueous sodium hydrogensulfite was added, and the mixture was stirred until it became colorless. The volatiles were removed under reduced pressure, and the residue was stirred with water to form a solid. The solid was isolated by filtration, washed with water, and recrystallized from ethanol and then from hexane to provide 2.5 g of 4-bromo-1,5-dimethyl-1*H*-pyrazole-3-carbonitrile as colorless needles, mp 92-94 °C.

Anal. Calcd. for $C_6H_6BrN_3$: C, 36.03; H, 3.02; N, 21.01. Found: C, 36.04; H, 2.86; N, 20.99.

Part D

Triphenylphosphine (2.4 mg, 0.09 mmol) and palladium (II) acetate (7 mg, 0.03 mmol) were added to a mixture of 4-bromo-1,5-dimethyl-1*H*-pyrazole-3-carbonitrile (0.600 g, 3.00 mmol), 2-aminophenylboronic acid (0.719 g, 5.25 mmol), aqueous sodium carbonate (1.8 mL of 2 M), propanol (5.25 mL) and water (1.1 mL). The reaction was heated under a nitrogen atmosphere at 100 °C for three hours and then allowed to cool to ambient temperature. The work-up procedure described in Part G of Examples 1-4 was followed. The resulting orange oil was purified by chromatography on a HORIZON HPFC system (25+M cartridge, eluting with ethyl acetate/hexane ranging in ratios from 50:50 to 75:25) to provide 371 mg of 4-(2-aminophenyl)-1,5-dimethyl-1*H*-pyrazole-3-carbonitrile as a pale yellow solid.

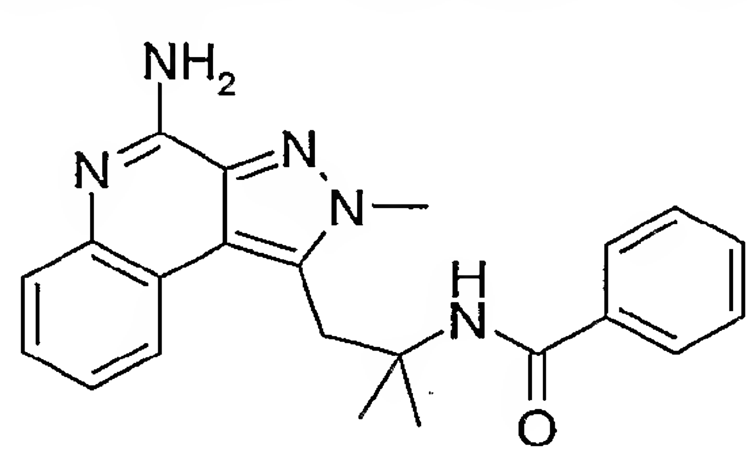
Part E

A solution of acetyl chloride (0.150 g, 1.9 mmol) in ethanol (6.4 mL) was stirred for 15 minutes. 4-(2-Aminophenyl)-1,5-dimethyl-1*H*-pyrazole-3-carbonitrile (O.270 g, 1.27 mmol) was added, and the reaction was heated at reflux under a nitrogen atmosphere for two hours. A precipitate formed. The mixture was allowed to cool to ambient temperature and then cooled to 0 °C. The solid was isolated by filtration, washed with diethyl ether, and dried to provide 285 mg of 1,2-dimethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine hydrochloride as a white solid, mp > 250 °C.

Anal. Calcd. for $C_{12}H_{12}N_4$•HCl: C, 57.95; H, 5.27; N, 22.53. Found: C, 57.78; H, 5.23; N, 22.34.

Example 6

N-[2-(4-Amino-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]benzamide



Part A

4-Methyl-4-benzamido-2-pentanone is available from the literature procedure (Scheuer, P. J. *et al.*, *J. Am. Chem. Soc.*, 1957, *22*, 674-676) or from the following method.

A mixture of mesityl oxide (19.6 g, 0.200 mol) and benzonitrile (22.0 g, 0.210 mol) was cooled to 0 °C; concentrated sulfuric acid (20 mL) was added in 2 mL increments over a period of ten minutes. The reaction was heated to 35 °C, and the reaction temperature rose quickly to 55 °C. The reaction temperature was maintained at between 50 and 55 °C for one hour. The viscous liquid was poured into ice water (800 mL), and the mixture was stirred for 90 minutes. A solid formed and was isolated by filtration, washed with water, washed with 2M aqueous sodium carbonate (100 mL), washed again with water until the filtrate was pH neutral, and dried under nitrogen overnight. The solid was then recrystallized from *tert*-butyl methyl ether (150 mL) to provide 19.0 g of 4-methyl-4-benzamido-2-pentanone as beige needles.

Part B

Sodium *tert*-butoxide (5.98 g, 62.2 mmol) was added to a solution of 4-methyl-4-benzamido-2-pentanone (12.4 g, 56.5 mmol) and ethyl diethoxyacetate (11.0 g, 62.2 mmol) in ethanol (40 mL), and the reaction was heated at reflux under a nitrogen atmosphere for 3.5 hours. The solvent was removed under reduced pressure, and the residue was partitioned between saturated aqueous ammonium chloride and *tert*-butyl methyl ether. The aqueous solution was extracted twice with *tert*-butyl methyl ether, and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 17.5 g of *N*-(6,6-diethoxy-1,1-dimethyl-3,5-dioxohexyl)benzamide as a brown oil.

Part C

Methyl hydrazine (2.60 g, 56.5 mmol) was added over a period of ten minutes to a solution of the material from Part B in ethanol (56 mL), and the reaction was stirred overnight at ambient temperature. The solvent was removed under reduced pressure, and the residue was purified by chromatography on a HORIZON HPFC system (FLASH 65I cartridge, eluting with ethyl acetate/hexanes ranging in ratios from 50:50 to 90:10) to provide 8.74 g of *N*-[1-(5-diethoxymethyl-2-methyl-2*H*-pyrazol-3-yl)-1,1-dimethylethyl]benzamide as a viscous, yellow oil.

Part D

Hydrochloric acid (40 mL of 1 M) was added to a solution of *N*-[1-(5-diethoxymethyl-2-methyl-2*H*-pyrazol-3-yl)-1,1-dimethylethyl]benzamide (8.7 g, 24 mmol)

in tetrahydrofuran (40 mL), and the reaction was stirred for ten minutes. *tert*-Butyl methyl ether and 2 M aqueous sodium carbonate (20 mL) were added. The aqueous layer was extracted twice with *tert*-butyl methyl ether, and the combined organic fractions were dried over magnesium sulfate and filtered. Hexane was added, and the cloudy mixture was stored overnight in the refrigerator. Crystals formed and were isolated in two crops by filtration to provide 5.24 g of *N*-[1-(5-formyl-2-methyl-2*H*-pyrazol-3-yl)-1,1-dimethylethyl]benzamide as a white powder, mp 150-151 °C.

Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.22; H, 6.89; N, 14.73.

Part E

The method described in Part F of Examples 1-4 was used to brominate *N*-[1-(5-formyl-2-methyl-2*H*-pyrazol-3-yl)-1,1-dimethylethyl]benzamide (4.87 g, 17.1 mmol). The crude product was recrystallized from 50:50 hexane/ethyl acetate (140 mL), and the crystals were washed with hexane and dried for two hours under nitrogen to provide 4.91 g of *N*-[1-(4-bromo-5-formyl-2-methyl-2*H*-pyrazol-3-yl)-1,1-dimethylethyl]benzamide as white crystals, mp 150-151 °C.

Anal. Calcd. for $C_{16}H_{18}N_3O_2Br$: C, 52.76; H, 4.98; N, 11.54. Found: C, 52.85; H, 5.33; N, 11.54.

Part F

The method described in Part G of Examples 1-4 was used to couple *N*-[1-(4-bromo-5-formyl-2-methyl-2*H*-pyrazol-3-yl)-1,1-dimethylethyl]benzamide (3.64 g, 10.0 mmol) and 2-aminophenylboronic acid hydrochloride (2.08 g, 12.0 mmol). The reaction was heated for 4 hours. The product was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting sequentially with ethyl acetate and 99:1 ethyl acetate/methanol) to provide 1.81 g of *N*-[1,1-dimethyl-2-(2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)ethyl]benzamide as an orange solid.

Part G

3-Chloroperoxybenzoic acid (2.12 g, available as a 77% pure mixture) (mCPBA) was added to a solution of *N*-[1,1-dimethyl-2-(2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)ethyl]benzamide (2.28 g, 6.36 mmol) in chloroform (25 mL), and the reaction was stirred for 45 minutes at ambient temperature. Brine and 2 M aqueous sodium carbonate

were added, and the aqueous layer was separated and extracted with chloroform (6 x). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure.

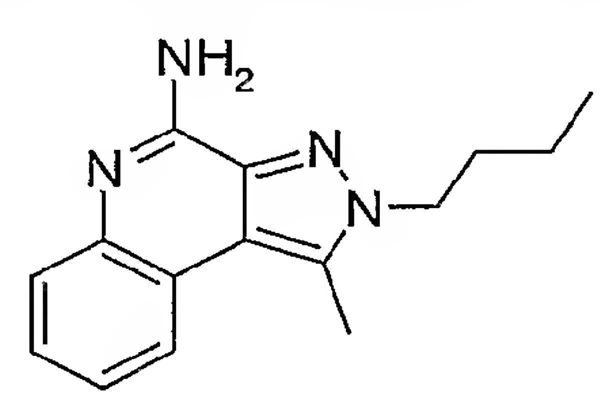
Part H

Under a nitrogen atmosphere, trichloroacetyl isocyanate (7.63 mmol) was added to a solution of the material from Part G in anhydrous dichloromethane (30 mL), and the reaction was stirred for 90 minutes at ambient temperature. The solvent was removed under reduced pressure. The residue was dissolved in methanol (15 mL), and a solution of sodium methoxide (1.5 mL, 25% in methanol) was added. The reaction was stirred for two hours, and then the solvent was removed under reduced pressure. The resulting oil was partitioned between dichloromethane and aqueous sodium chloride. The aqueous layer was extracted with dichloromethane (5 x), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow solid was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with chloroform/CMA ranging in ratios from 100:0 to 70:30) and recrystallized twice from acetonitrile (23 mL/g and 14 mL/g). The crystals were dried overnight at 6.65 Pa and 98 °C to provide 687 mg of *N*-[2-(4-amino-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]benzamide as beige needles, mp 194-196 °C.

Anal. Calcd. for $C_{22}H_{23}N_5O$: C, 70.76; H, 6.21; N, 18.75. Found: C, 70.54; H, 6.09; N, 18.85.

Example 7

2-Butyl-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Butylhydrazine oxalate (25 g, 140 mmol) was added over a period of 15 minutes to a solution of ethyl 2,4-dioxovalerate (22.2 g, 140 mmol) and triethylamine (210 mmol) in

ethanol (140 mL). The resulting solution was stirred overnight at ambient temperature and concentrated under reduced pressure. Hexane was added, and an insoluble solid was removed by filtration. The hexane was removed under reduced pressure; the residue was purified by chromatography on a HORIZON HPFC system (65I cartridge, eluting with hexanes/ethyl acetate in a gradient from 80:20 to 45:55) to provide 18.1 g of ethyl 1-butyl-5-methyl-1*H*-pyrazole-3-carboxylate as a pale yellow oil.

Part B

A solution of ethyl 1-butyl-5-methyl-1*H*-pyrazole-3-carboxylate (18.1 g, 86.1 mmol) in methanol (25 mL) was treated with ammonium hydroxide (25 mL) according to a modification of the method described in Part D of Examples 1-4. At the end of the reaction, the methanol was removed under reduced pressure, and the remaining solution was cooled in a refrigerator. A precipitate formed, was isolated by filtration, and was washed with water. The solid (9 g) was recrystallized from hexane (300 mL) and ethyl acetate (30 mL), isolated by filtration, washed with hexane, and air-dried to provide 6.95 g of 1-butyl-5-methyl-1*H*-pyrazole-3-carboxamide as colorless plates, mp 113.5-114.5 °C. Anal. Calcd for $C_9H_{15}N_3O$: C, 59.65; H, 8.34; N, 23.18. Found: C, 59.79; H, 8.21; N, 23.28.

Part C

A mixture of 1-butyl-5-methyl-1*H*-pyrazole-3-carboxamide (6.9 g, 38 mmol) and phosphorous oxychloride (34.0 mL) was heated at 90 °C under a nitrogen atmosphere for two hours and then allowed to cool to ambient temperature overnight. The reaction was poured into ice water (300 mL); concentrated ammonium hydroxide (115 mL) was added. The mixture was extracted with chloroform (3 x), and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 6.58 g of 1-butyl-5-methyl-1*H*-pyrazole-3-carbonitrile as a pale yellow oil.

Part D

1-Butyl-5-methyl-1*H*-pyrazole-3-carbonitrile (6.58 g, 38 mmol) was treated with potassium acetate (57.2 mmol) and bromine (41.9 mmol) in acetic acid (50 mL) according to a modification of the method described in Part F of Examples 1-4. The reaction provided 9.3 g of 4-bromo-1-butyl-5-methyl-1*H*-pyrazole-3-carbonitrile as a colorless oil that crystallized upon standing. The crystals were used without purification.

Part E

A modification of the method described in Part G of Examples 1-4 was used to couple 4-bromo-1-butyl-5-methyl-1*H*-pyrazole-3-carbonitrile (2.42 g, 10.0 mmol) and 2-aminophenylboronic acid hydrochloride (2.43 g, 14.0 mmol). Palladium (II) acetate was added as a 5 mg/mL solution in toluene (1.3 mL). The reaction was heated under nitrogen for 17 hours and combined with the product mixture from another run before being subjected to the work-up procedure. The crude product was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with chloroform:CMA in a gradient from 100:0 to 80:20) to provide 3.17 g of 4-(2-aminophenyl)-1-butyl-5-methyl-1*H*-pyrazole-3-carbonitrile as an orange oil. A small amount (0.21 g) of 2-butyl-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was also obtained as a beige powder.

Part F

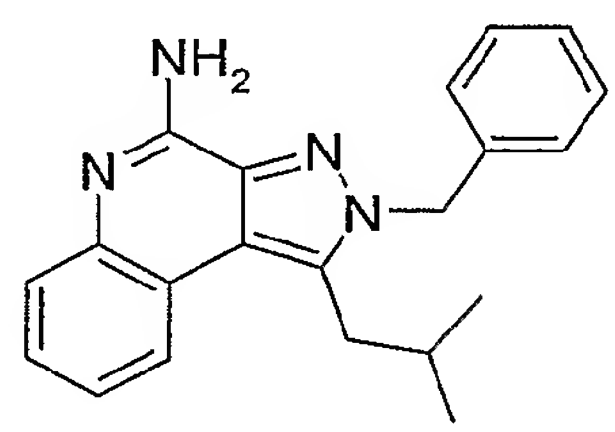
Acetyl chloride (15 mmol) and ethanol (50 mL) were combined and added to 4-(2-aminophenyl)-1-butyl-5-methyl-1*H*-pyrazole-3-carbonitrile (3.17 g) according to the method described in Part H of Examples 1-4. The reaction was heated for 16 hours. Following the work-up procedure, chromatographic purification, and recrystallization from acetonitrile (195 mL/g) 873 mg of 2-butyl-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine were obtained as white needles, mp 220-222 °C.

MS (APCI) m/z 255 $(M + H)^+$;

Anal. Calcd for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.64; H, 6.94; N, 22.14.

Example 8

2-Benzyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Potassium acetate (49.1 g, 0.500 mol) was added with stirring to a solution of ethyl 6-methyl-2,4-dioxoheptanoate, sodium salt (44.4 g, 0.200 mol), prepared as described in

Part A of Examples 1-4, in acetic acid (280 mL). The solution was cooled to 10 °C, and benzylhydrazine dihydrochloride (39.0 g, 0.200 mol) was added in portions over a period of ten minutes while the reaction temperature was maintained between 10 °C and 13.5 °C. The reaction was stirred for 90 minutes at between 6 °C and 13.6 °C, allowed to warm to ambient temperature, stirred overnight, and concentrated under reduced pressure. The residue was partitioned between 2 M aqueous sodium carbonate (900 mL) and *tert*-butyl methyl ether (600 mL). The aqueous layer was extracted with *tert*-butyl methyl ether (2 x 300 mL), and the combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 56.6 g of ethyl 1-benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carboxylate as an oil orange. The product contained 10 mol% of ethyl 2-benzyl-5-(2-methylpropyl)-2*H*-pyrazole-3-carboxylate.

Part B

A solution of ethyl 1-benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carboxylate (30 g) in methanol (60 mL) was treated with ammonium hydroxide (60 mL) according to a modification of the method described in Part D of Examples 1-4. The reaction was heated for 14 hours. At the end of the reaction, the methanol was removed under reduced pressure, and the remaining solution was extracted with *tert*-butyl methyl ether (3 x). The combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Toluene was added twice and removed under reduced pressure to remove residual water. Hexane was added to the residue; crystals formed and were isolated by filtration, washed with hexane, and air-dried overnight to provide 6.93 g of 1-benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carboxamide as small, off-white crystals.

Part C

A mixture of 1-benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carboxamide (6.77 g, 26.3 mmol) and phosphorous oxychloride (19 mL) was heated at 90 °C under a nitrogen atmosphere for 90 minutes and then allowed to cool to ambient temperature. The reaction was poured into ice water (250 mL); concentrated ammonium hydroxide (64 mL) was added. The mixture was extracted with *tert*-butyl methyl ether (3 x 150 mL), and the combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 6.28 g of 1-benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile as a pale orange oil.

Part D

1-Benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile (6.28 g, 26.2 mmol) was treated with potassium acetate (3.9 g, 39 mmol) and bromine (4.61 g, 28.8 mmol) in acetic acid (52 mL) according to the method described in Part F of Examples 1-4. Following chromatographic purification (eluting with hexanes/ethyl acetate in a gradient from 95:5 to 70:30) 7.8 g of 4-bromo-1-benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile were obtained as a colorless oil containing 11 mol% of the starting material.

Part E

The method described in Part G of Examples 1-4 was used to couple 4-bromo-1-benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile (3.18 g, 10.0 mmol) and 2-aminophenylboronic acid hydrochloride (2.60 g, 15.0 mmol) in the presence of palladium (II) acetate (22.5 mg), triphenylphosphine (79 mg), and 2 M aqueous sodium carbonate (15 mL). The product, 4-2(-aminophenyl)-1-benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile, was used without purification.

Part F

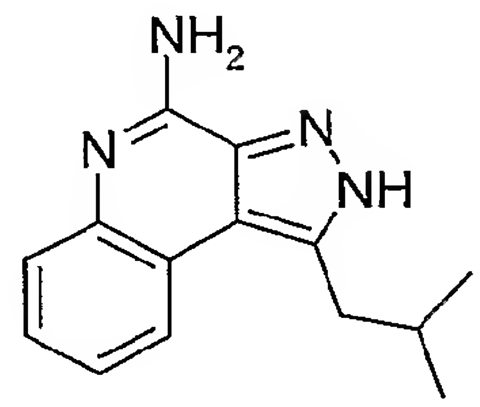
The material from Part E was treated according to the method described in Part H of Examples 1-4. Following the work-up procedure and chromatographic purification (eluting with chloroform/CMA in a gradient from 97:3 to 87:13), 1.81 g of product were obtained as a beige solid. A portion (0.63 g) was recrystallized from acetonitrile (28.6 mL/g), isolated by filtration, washed with acetonitrile, and dried for 36 hours in a vacuum oven at 65 °C to provide 559 mg of 2-benzyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as large, beige needles, mp 194-196 °C.

MS (APCI) m/z 331 $(M + H)^+$;

Anal. Calcd for $C_{21}H_{22}N_4$: C, 76.33; H, 6.71; N, 16.96. Found: C, 76.03; H, 6.84; N, 16.97.

Example 9

1-(2-Methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



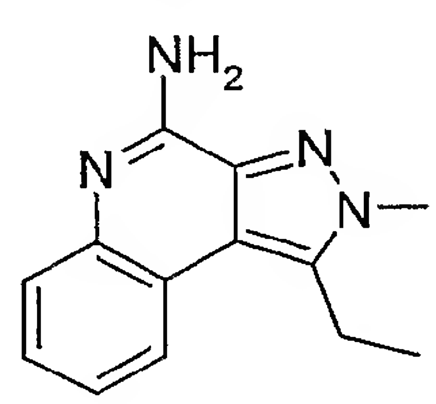
Hydrogen bromide (10 mL of 30% by weight in acetic acid) and 2-benzyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (0.75 g, 2.27 mmol) were combined in a TEFLON-lined Parr vessel and heated at 150 °C for 24 hours and then allowed to cool to ambient temperature over five hours. The reaction was filtered to remove a solid, and the filtrate was adjusted to pH 7 with the addition of 50% sodium hydroxide and 2M aqueous sodium carbonate. A precipitate formed and was isolated by filtration, washed with water, and air-dried. The solid was purified by chromatography on a HORIZON HPFC system (25+M cartridge, eluting with chloroform/CMA in a gradient from 80:20 to 40:60) followed by recrystallization from acetonitrile (19 mL/g) and a small amount of methanol. The crystals were isolated by filtration, washed with acetonitrile, and dried for 36 hours in a vacuum oven at 65 °C to provide 139 mg of 1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as small, pale orange needles, mp 248-249 °C.

MS (APCI) m/z 241 $(M + H)^+$;

Anal. Calcd for $C_{14}H_{16}N_4 \cdot 0.17\ CH_3OH \cdot 0.16H_2O$: C, 68.45; H, 6.89; N, 22.53. Found: C, 68.43; H, 6.87; N, 22.53.

Example 10

1-Ethyl-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Sodium *tert*-butoxide (66.64 g, 0.693 mol) was added over a period of 20 minutes to ethanol (450 mL) under a nitrogen atmosphere. When all solids had dissolved, a

mixture of diethyl oxalate (101.28 g, 0.693 mol) and 2-butanone (50.0 g, 0.693 mol) was added over a period of 12 minutes. The reaction was stirred at ambient temperature for 1.5 hours and then used in the next step.

Part B

The solution from Part A was treated with glacial acetic acid (115 mL) and then cooled to 0 °C. Methylhydrazine (36.5 mL, 0.693 mmol) was slowly added over a period of 20 minutes. The reaction was allowed to warm to ambient temperature, stirred for two hours, and concentrated under reduced pressure. The residue was made basic with the addition of 2 M aqueous sodium carbonate and extracted with *tert*-butyl methyl ether (3 x 400 mL). The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 100 g of a red oil. Half of the oil was purified by chromatography on a HORIZON HPFC system (eluting with hexanes:ethyl acetate in a gradient from 100:0 to 0:100 to provide 6.53 g of ethyl 5-ethyl-1-methyl-1*H*-pyrazole-3-carboxylate as a yellow oil.

Part C

A mixture of ethyl 5-ethyl-1-methyl-1*H*-pyrazole-3-carboxylate (5.03 g, 27.6 mmol) and ammonium hydroxide (28 mL of 30%) was stirred for 18 hours at ambient temperature. A precipitate formed, was isolated by filtration, and washed with cold hexanes to provide 2.60 g of 5-ethyl-1-methyl-1*H*-pyrazole-3-carboxamide as a white solid, mp 170-172 °C.

Anal. Calcd for $C_7H_{11}N_3O$: C, 54.89; H, 7.24; N, 27.43. Found: C, 54.87; H, 7.56; N, 27.58.

The product was mixed with material from another run.

Part D

5-Ethyl-1-methyl-1*H*-pyrazole-3-carboxamide (3.8 g, 25 mmol) was treated with phosphorous oxychloride (18 mL, 0.19 mol) according to the method described in Part C of Example 8 to provide 2.68 g of 5-ethyl-1-methyl-1*H*-pyrazole-3-carbonitrile as a yellow oil.

Part E

5-Ethyl-1-methyl-1*H*-pyrazole-3-carbonitrile (2.68 g, 19.8 mmol) was treated with potassium acetate (2.91 g, 29.7 mmol) and bromine (3.16 g, 19.8 mmol) in acetic acid (25

mL) according to a modification of the method described in Part F of Examples 1-4. The extraction was carried out with *tert*-butyl methyl ether, and the combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 3.8 g of a white solid. A small portion of the solid was recrystallized from ethanol to provide 4-bromo-5-ethyl-1-methyl-1*H*-pyrazole-3-carbonitrile as long, white needles, mp 72-74 °C.

Anal. Calcd for $C_7H_8BrN_3$: C, 39.28; H, 3.77; N, 19.63. Found: C, 39.26; H, 3.55; N, 19.63.

Part F

A modification of the method described in Part G of Examples 1-4 was used to couple 4-bromo-5-ethyl-1-methyl-1*H*-pyrazole-3-carbonitrile (1.65 g, 7.7 mmol) and 2-aminophenylboronic acid hydrochloride (2.01 g, 11.6 mmol) in the presence of palladium (II) acetate (17.3 mg, 0.077 mmol), triphenylphosphine (60.6 mg, 0.23 mmol), and 2 M aqueous sodium carbonate (11.6 mL). At the end of the reaction, *tert*-butyl methyl ether was added. The aqueous phase was separated and extracted with *tert*-butyl methyl ether (2 x); the combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide a mixture of 4-(2-aminophenyl)-5-ethyl-1-methyl-1*H*-pyrazole-3-carbonitrile and 1-ethyl-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine.

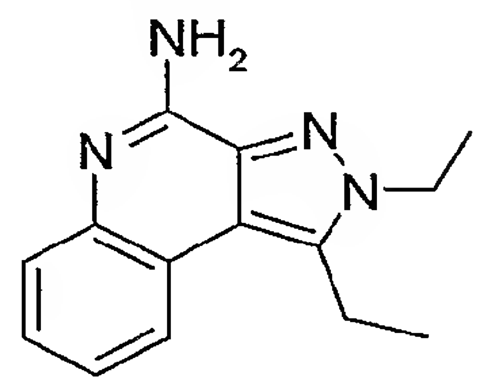
Part G

Ethanol (12 mL) was cooled to 0 °C, and acetyl chloride (0.91 g, 12 mmol) was added. The solution was allowed to warm to ambient temperature and stirred for 30 minutes. A suspension of the material from Part F in ethanol (5 mL) was added, and the mixture was heated at reflux for four hours. The reaction was allowed to cool to ambient temperature. A precipitate was present, isolated by filtration, and combined with material from another run. Chloroform (4 mL) and 2 M aqueous sodium carbonate were added, and the mixture was stirred for six hours. A precipitate formed and was isolated by filtration, washed sequentially with cold water and cold hexanes, and dried in a vacuum oven at 60 °C to provide 0.85 g of 1-ethyl-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white solid, mp 257-259 °C.

Anal. Calcd for $C_{13}H_{14}N_4$•0.2 H_2O: C, 67.92; H, 6.31; N, 24.37. Found: C, 67.69; H, 6.40; N, 24.76.

Example 11

1,2-Diethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A solution of ethyl 2,4-dioxohexanoate (~0.345 mol), prepared as described in Part A of Example 10, in glacial acetic acid (350 mL) was cooled to 0 °C. Ethylhydrazine oxalate (41.43 g, 0.276 mol) was added over a period of 20 minutes. The reaction was allowed to warm to ambient temperature, stirred for 20 hours, and concentrated under reduced pressure. The residue was adjusted to pH 10 with the addition of 2 M aqueous sodium carbonate, and chloroform was added. The mixture was filtered to remove a solid. The aqueous filtrate was extracted with chloroform (3 x), and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 29.4 g of ethyl 1,5-diethyl-1*H*-pyrazole-3-carboxylate as an orange oil, which was used without purification.

Part B

A mixture of ethyl 1,5-diethyl-1*H*-pyrazole-3-carboxylate (29.4 g, 0.150mol) and ammonium hydroxide (150 mL of 30%) was stirred overnight at ambient temperature. An analysis by thin layer chromatography (TLC) indicated the reaction was incomplete. The reaction was then heated for 14 hours at 125 °C in a pressure vessel, allowed to cool to ambient temperature, and cooled to 0 °C. A precipitate formed, was isolated by filtration, and washed with cold hexanes to provide 8.3 g of 1,5-diethyl-1*H*-pyrazole-3-carboxamide as a white solid, mp 129-131 °C.

Anal. Calcd for $C_8H_{13}N_3O$: C, 57.47; H, 7.84; N, 25.13. Found: C, 57.37; H, 8.04; N, 25.43.

Part C

1,5-Diethyl-1*H*-pyrazole-3-carboxamide (8.3 g, 0.050 mol) was treated with phosphorous oxychloride (35 mL) according to the method described in Part C of Example 7. The reaction was heated for 2.5 hours to provide 7.6 g of 1,5-diethyl-1*H*-pyrazole-3-carbonitrile as a yellow oil, which was used without purification.

Part D

The material from Part C was treated with potassium acetate (7.30 g, 7.44 mmol) and bromine (7.92 g, 49.6 mmol) in acetic acid (60 mL) according to a modification of the method described in Part F of Examples 1-4. The reaction was cooled in an ice bath during the addition of bromine. After the addition, the reaction was stirred at ambient temperature over three days. The extraction was carried out with chloroform (3 x 100 mL), and the combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 9.4 g of 4-bromo-1,5-diethyl-1*H*-pyrazole-3-carbonitrile as an orange oil, which crystallized to an orange solid. The product was used without purification.

Part E

4-Bromo-1,5-diethyl-1*H*-pyrazole-3-carbonitrile (4.56 g, 20.0 mmol) and 2-aminophenylboronic acid hydrochloride (5.20 g, 30.0 mmol) were coupled in the presence of palladium (II) acetate (45 mg, 0.20 mmol), triphenylphosphine (157 mg, 0.599 mmol), and 2 M aqueous sodium carbonate (30 mL) according to the method described in Part F of Example 10. The product, 4-(2-aminophenyl)-1,5-diethyl-1*H*-pyrazole-3-carbonitrile, was used without purification.

Part F

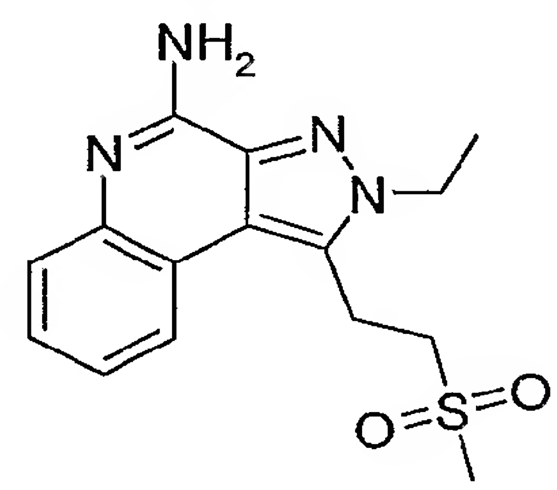
The material from Part E was added to a solution of acetyl chloride (2.36 g, 30.0 mmol) in ethanol (30 mL) according to a modification of the method described in Part G of Example 10. The reaction was heated at reflux for six hours and then heated at 81 °C overnight. The crude product was purified by chromatography on a HORIZON HPFC system (eluting with a gradient of chloroform/CMA) followed by recrystallization from acetonitrile. The crystals were heated a second time in acetonitrile in the presence of activated charcoal, which was removed by hot filtration, and recrystallized to provide

0.440 g of 1,2-diethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as an off-white crystalline solid, mp 234-236 °C.

Anal. Calcd for $C_{14}H_{16}N_4$: C, 69.97; H, 6.71; N, 23.31. Found: C, 69.93; H, 7.03; N, 23.61.

Example 12

2-Ethyl-1-(2-methanesulfonylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Diethyl oxalate (19.8 g, 135 mmol) and 4-methylthio-2-butanone (16 g, 135 mmol) were added to a solution of potassium *tert*-butoxide (13 g, 135 mmol) in ethanol (97 mL) according to the method described in Part A of Example 10.

Part B

Acetic acid (38 mL) and potassium acetate (20 g, 200 mmol) were sequentially added to the solution from Part A. The resulting suspension was cooled to 0 °C, and ethylhydrazine oxalate (20.3 g, 135 mmol) was added with vigorous stirring over a period of ten minutes. The reaction was stirred for 15 minutes at 0 °C and for one hour at ambient temperature and then concentrated under reduced pressure. Saturated aqueous sodium carbonate was added to adjust the residue to pH 9, and water was added. The mixture was extracted with dichloromethane (2 x 100 mL), and the combined extracts were washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluting with 1:1 ethyl acetate/hexanes) to provide 8.8 g of ethyl 1-ethyl-5-(2-methylsulfanylethyl)-1*H*-pyrazole-3-carboxylate as an orange oil.

Part C

mCPBA (17.9 g, 72.6 mmol, ~70% pure) was added in portions to a solution of ethyl 1-ethyl-5-(2-methylsulfanylethyl)-1*H*-pyrazole-3-carboxylate (8.8 g, 36 mmol) over a

period of 15 minutes. The reaction was then stirred at ambient temperature for 20 minutes and partitioned between chloroform (100 mL) and saturated aqueous sodium carbonate (100 mL). The organic layer was separated and washed with brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluting with ethyl acetate) to provide 4.6 g of ethyl 1-ethyl-5-(2-methanesulfonylethyl)-1*H*-pyrazole-3-carboxylate as a white solid.

Part D

The method described in Part C of Example 10 was used to treat ethyl 1-ethyl-5-(2-methanesulfonylethyl)-1*H*-pyrazole-3-carboxylate (4.6 g, 17 mmol) with ammonium hydroxide (100 mL). The solid was isolated by filtration and washed with water to provide 3.0 g of 1-ethyl-5-(2-methanesulfonylethyl)-1*H*-pyrazole-3-carboxamide as a white powder, which was mixed with material from another run.

Part E

A modification of the method described in Part E of Examples 1-4 was used to treat 1-ethyl-5-(2-methanesulfonylethyl)-1*H*-pyrazole-3-carboxamide (3.46 g, 14.1 mmol) with phosphorous oxychloride (10 mL). The reaction was heated for 2.5 hours. After the addition of ammonium hydroxide (35 mL of 28%) a precipitate formed. The mixture was stirred for 30 minutes, and the precipitate was isolated by filtration and washed with water to provide 3.1 g of 1-ethyl-5-(2-methanesulfonylethyl)-1*H*-pyrazole-3-carbonitrile as a white powder.

Part F

A modification of the method described in Part F of Examples 1-4 was used to treat a solution of 1-ethyl-5-(2-methanesulfonylethyl)-1*H*-pyrazole-3-carbonitrile (3.1 g, 14 mmol) in acetic acid (27 mL) with potassium acetate (2 g, 20 mmol) and bromine (2.2 g, 14 mmol). The reaction was stirred for 20 minutes before the addition of aqueous sodium hydrogensulfite (1 mL). After the addition of saturated aqueous sodium carbonate, a precipitate formed, was isolated by filtration, and washed with water to provide 2.4 g of a 2:1 mixture of 4-bromo-1-ethyl-5-(2-methanesulfonylethyl)-1*H*-pyrazole-3-carbonitrile and 1-ethyl-5-(2-methanesulfonylethyl)-1*H*-pyrazole-3-carbonitrile, which was used without purification.

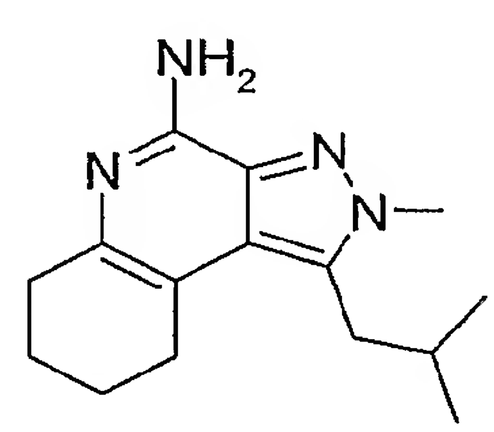
Part G

Triphenylphosphine (6.1 mg, 0.023 mmol) and palladium (II) acetate (1.75 mg, 0.0018 mmol) were added to a mixture of the material from Part F, 2-aminophenylboronic acid hydrochloride (2.03 g, 11.8 mmol), 2 M aqueous sodium carbonate (23 mL), water (3 mL) and *n*-propanol (14 mL) according to a modification of the method described in Part G of Examples 1-4. The work-up procedure was carried out by partitioning between dichloromethane (100 mL) and saturated aqueous sodium carbonate (50 mL) and extracting with dichloromethane (50 mL). Following the work-up procedure, the crude product mixture was triturated with ethyl acetate, and a white solid was removed by filtration. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (eluting with 90:10 dichloromethane/methanol) followed by recrystallization from acetonitrile. The crystals were isolated by filtration, washed with acetonitrile, and dried under vacuum for 20 hours at 60 °C to provide 0.05 g of 2-ethyl-1-(2-methanesulfonylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as pale yellow needles, mp 220-222 °C.

Anal. Calcd for $C_{15}H_{18}N_4O_2S{\cdot}0.25\ H_2O$: C, 55.80; H, 5.77; N, 17.35. Found: C, 55.71; H, 5.60; N, 17.41.

Example 13

2-Methyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine trifluoroacetate



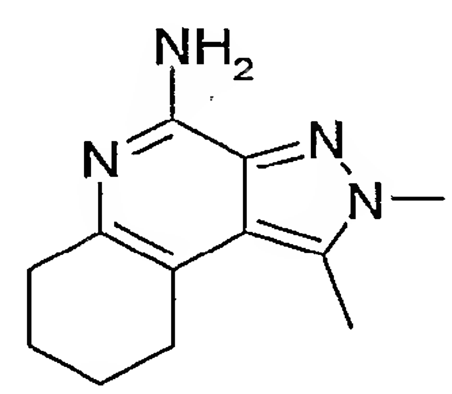
A solution of 2-methyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (0.6 g, 2 mmol), prepared as described in Example 3, in trifluoroacetic acid (10 mL) was treated with platinum (IV) oxide (0.5 g) and shaken under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) for 24 hours. The reaction mixture was diluted with chloroform (20 mL) and filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure and dissolved in chloroform (50 mL). The solution was adjusted to pH

12 with the addition of ammonium hydroxide and stirred for 20 minutes. The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was recrystallized from acetonitrile to provide 0.3 g of 2-methyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine trifluoroacetate as a white powder, mp 204-206 °C.

Anal. Calcd for $C_{15}H_{22}N_4$•0.76 CF_3COOH: C, 57.51; H, 6.65; N, 16.24. Found: C, 57.11; H, 7.04; N, 16.23.

Example 14

1,2-Dimethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine

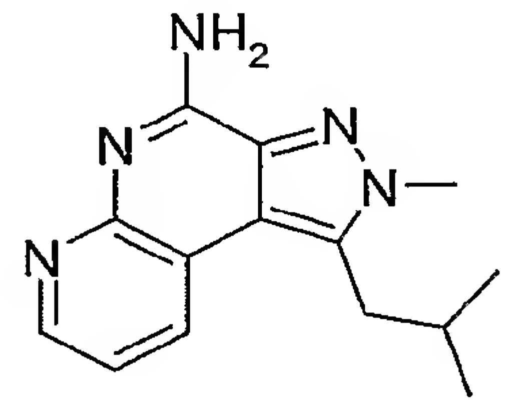


A modification of the method described in Example 13 was used to reduce 1,2-dimethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (1.0 g, 4.7 mmol), prepared as described in Example 5. During the work-up procedure, the residue from the filtrate was suspended in 6 M hydrochloric acid and stirred for 30 minutes. The suspension was adjusted to pH 13 with the addition of 50% sodium hydroxide. The resulting solid was isolated by filtration, washed with water, air-dried, and recrystallized from acetonitrile to provide 0.74 g of 1,2-dimethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as an off-white solid, mp 258-259 °C.

Anal. Calcd for $C_{12}H_{16}N_4$•0.1 H_2O: C, 66.09; H, 7.49; N, 25.69. Found: C, 65.87; H, 7.52; N, 25.51.

Example 15

2-Methyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*][1,8]naphthyridin-4-amine



Part A

tert-Butyl *N*-(2-pyridyl)carbamate is available from the literature procedure (Moraczewski, A. L. *et al*, *J. Org. Chem.*, 1998, *63*, 7258) or can be prepared by the following method. Under a nitrogen atmosphere, sodium bis(trimethylsilyl)amide (225 mL of a 1.0 M solution in tetrahydrofuran) was added over a period of 20 minutes to a solution of 2-aminopyridine (10.61 g, 108.0 mmol) in dry tetrahydrofuran (THF) (150 mL). The solution was stirred for 15 minutes and then cooled to 0 °C. A solution of di-*tert*-butyl dicarbonate (24.60 g, 1 12.7 mmol) in THF (50 mL) was added slowly, and the reaction was allowed to warm to ambient temperature slowly and stirred overnight. The THF was removed under reduced pressure, and the residue was partitioned between ethyl acetate (500 mL) and 0.1 M hydrochloric acid (250 mL). The organic layer was separated; washed sequentially with 0.1 M hydrochloric acid (250 mL), water (250 mL), and brine (250 mL); dried over magnesium sulfate; filtered; and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (65I cartridge, eluting with 80:20 hexanes/ethyl acetate to provide 17.43 g of *tert*-butyl *N*-(2-pyridyl)carbamate as a white solid.

Part B

Under a nitrogen atmosphere, a solution of *tert*-butyl *N*-(2-pyridyl)carbamate (15.71 g, 80.9 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA, 25.3 g, 218 mmol) in THF (400 mL) was cooled to -78 °C. *n*-Butyllithium (81 mL of a 2.5 M solution in hexanes) was added dropwise over a period of 20 minutes. The solution was stirred for ten minutes, and then the addition funnel was rinsed with additional THF (20 mL). The solution was warmed to -6 °C, stirred for two hours, and cooled again to -78 °C. Triisopropyl borate (57.7 g, 307 mmol) was added over a period of ten minutes. The resulting solution was warmed to 0 °C and then poured into saturated aqueous ammonium

chloride (500 mL). A yellow solid formed and was stirred with diethyl ether (300 mL), isolated by filtration, washed with diethyl ether and water, and air-dried overnight to provide 2-*tert*-butoxycarbonylamino-3-pyridylboronic acid as a yellow solid.

Part C

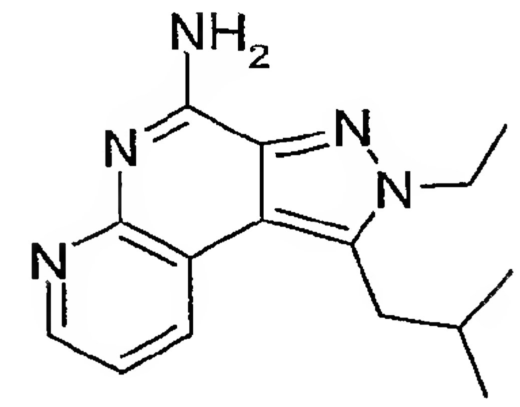
A solution of 2-*tert*-butoxycarbonylamino-3-pyridylboronic acid (7.2 g) and hydrogen chloride (4 M in ethanol) was heated at reflux for 20 minutes. Toluene (50 mL) was added, and the solvents were removed by distillation. The resulting oil was dissolved in water and adjusted to pH 8 with the addition of 2 M aqueous sodium carbonate. The resulting solution was concentrated under reduced pressure to a volume of 20 mL.

Part D

4-Bromo-1-methyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile (2.42 g, 10.0 mmol), prepared as described in Example 3, solid sodium carbonate (1.6 g, 15 mmol), 1-propanol (25 mL), palladium (II) acetate (22 mg, 0.1 mmol), and triphenylphosphine (79 mg, 0.3 mmol) were added to the solution from Part C, and the reaction was heated at 100 °C under a nitrogen atmosphere for 6.5 hours. Additional palladium (II) acetate (22 mg, 0.1 mmol) and triphenylphosphine (79 mg, 0.3 mmol) were added, and the reaction was heated at 100 °C overnight. The work-up procedure described in Part G of Examples 1-4 was followed. The crude product was obtained as a semi-solid and was stirred with *tert*-butyl methyl ether to form a solid, which was isolated by filtration. The solid was purified by chromatography on a HORIZON HPFC system (40+M cartridge (eluting with acetone/methanol in a gradient from 99:1 to 85:1). The resulting solid (450 mg) was triturated with hot acetonitrile (10 mL), cooled to 0 °C, isolated by filtration, and air-dried to provide 365 mg of 2-methyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*][1,8]naphthyridin-4-amine as a white powder, mp >250 °C. MS (APCI) m/z 256 $(M + H)^+$; Anal. Calcd for $C_{14}H_{17}N_5 \cdot 0.4H_2O$: C, 64.05; H, 6.83; N, 26.68. Found: C, 64.04; H, 7.27; N, 26.70.

Example 16

2-Ethyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*][1,8]naphthyridin-4-amine

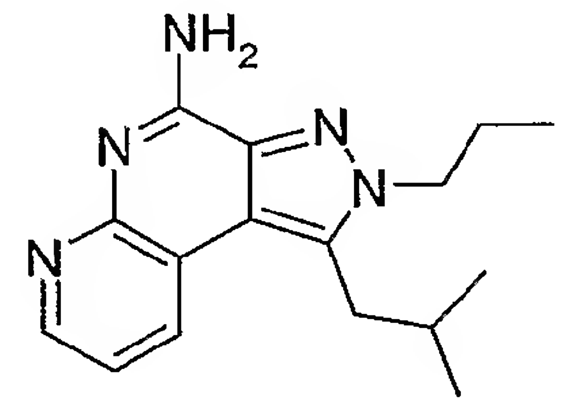


Hydrochloric acid (15 mL of 1M) was added to a solution of 2-*tert*-butoxycarbonylamino-3-pyridylboronic acid (3.31 g, 13.9 mmol), prepared as described in Parts A and B of Example 15, in 1-propanol (15 mL), and the resulting mixture was heated at 80 °C for one hour and allowed to cool to ambient temperature. Solid sodium carbonate (2.69 g, 25.4 mmol) was added with stirring followed by a solution of 4-bromo-1-ethyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile (1.78 g, 6.95 mmol), prepared as described in Example 2, in 1-propanol (4 mL). Triphenylphosphine (109 mg, 0.42 mmol) was added, and the reaction was evacuated and backfilled with nitrogen three times and stirred for five minutes. A solution of palladium (II) acetate (31 mg, 0.14 mmol) in warm toluene (0.5 mL) was added. The reaction was twice evacuated and backfilled with nitrogen and then heated at 100 °C overnight. An analysis by HPLC indicated the reaction was incomplete, and additional triphenylphosphine (109 mg, 0.42 mmol) and palladium (II) acetate (31 mg, 0.14 mmol) were added. The reaction was twice evacuated and backfilled with nitrogen at heated at reflux for three days. The 1-propanol was removed under reduced pressure, and the residue was dissolved in chloroform (100 mL). The resulting solution was washed with water, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system as described in Example 15. The resulting solid (200 mg) was recrystallized from acetonitrile (20 mL) after hot filtration, isolated by filtration, washed with cold acetonitrile, and dried overnight in a vacuum oven at 60 °C to provide 0.17 g of 2-ethyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*][1,8]naphthyridin-4-amine as off-white needles, mp 273-276 °C.

Anal. Calcd for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00. Found: C, 66.77; H, 6.94; N, 26.34.

Example 17

1-(2-Methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*][1,8]naphthyridin-4-amine

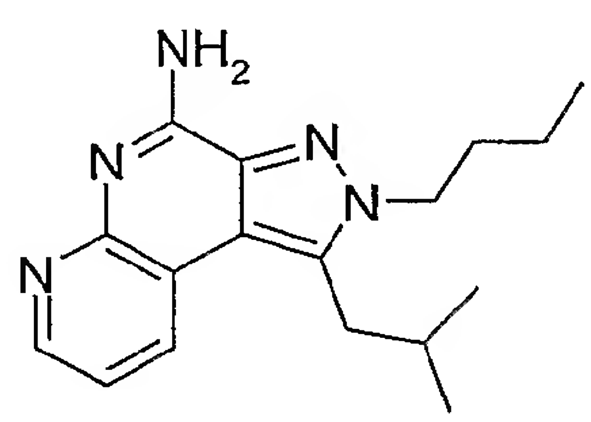


A modification of the method described in Example 16 was used to treat 2-*tert*-butoxycarbonylamino-3-pyridylboronic acid (11.33 mmol) in 1-propanol (10 mL) with hydrochloric acid (12 mL of 1 M) followed by sodium carbonate (1.99 g, 18.8 mmol), 4-bromo-5-(2-methylpropyl)-1-propyl-1*H*-pyrazole-3-carbonitrile (1.53 g, 5.66 mmol, prepared as described in Example 1) in 1-propanol (5 mL), triphenylphosphine (44.5 mg, 0.17 mmol), and palladium (II) acetate (13 mg, 0.057 mmol) in toluene (0.25 mL). The reaction was complete after it was heated overnight. Following the work-up procedure and purification, 0.18 g of 1-(2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*][1,8]naphthyridin-4-amine was obtained as off-white needles, mp 257-260 °C.

Anal. Calcd for $C_{16}H_{21}N_5$: C, 67.82; H, 7.47; N, 24.71. Found: C, 67.77; H, 7.59; N, 24.52.

Example 18

2-Butyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*][1,8]naphthyridin-4-amine



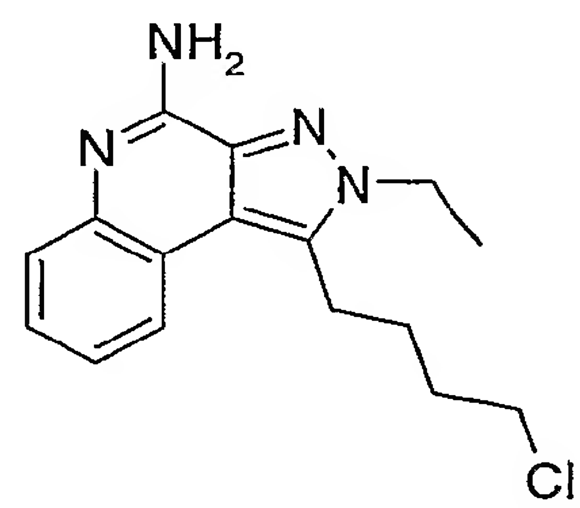
A modification of the method described in Example 16 was used to treat 2-*tert*-butoxycarbonylamino-3-pyridylboronic acid (2.98 g, 12.5 mmol) in 1-propanol (15 mL) with hydrochloric acid (15 mL of 1 M) followed by sodium carbonate (2.66 g, 25.1 mmol), 4-bromo-1-butyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile (1.91 g, 6.72 mmol, prepared as described in Example 4) in 1-propanol (4 mL), triphenylphosphine (105 mg, 0.400 mmol), and palladium (II) acetate (30 mg, 0.13 mmol). The reaction was complete after it was heated over two nights, and no additional reagents were added. Following the

work-up procedure and purification, the crude solid was purified by chromatography on a HORIZON HPFC system (eluting with chloroform/CMA in a gradient from 100:0 to 75:25 to provide 0.48 g of a light yellow solid, which was recrystallized and isolated as described in Example 16 to provide 0.29 g of 2-butyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*][1,8]naphthyridin-4-amine as off-white needles, mp 219-222 °C.

Anal. Calcd for $C_{17}H_{23}N_5$: C, 66.86; H, 7.80; N, 23.55. Found: C, 68.56; H, 8.05; N, 23.88.

Example 19

1-(4-Chlorobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Under a nitrogen atmosphere, a mixture sodium *tert*-butoxide (39.0 g, 0.406 mol) and ethanol (135 mL) was stirred for 30 minutes; most of the solid was dissolved. A solution of diethyl oxalate (25.6 mL, 0.189 mol) and 6-chloro-2-hexanone (25.6 mL, 0.189 mol) in ethanol (20 mL) was added over a period of 20 minutes. The reaction was stirred at ambient temperature for one hour, and potassium acetate (28.0 g, 283 mmol) and acetic acid (95 mL of 2 M) were sequentially added. The reaction was cooled to 0 °C, and ethylhydrazine oxalate (31.0 g, 208 mmol) was added in one portion. The reaction was allowed to warm to ambient temperature, stirred for two hours, and then concentrated under reduced pressure. Water was added, and the resulting solution was adjusted to pH 11 with the addition of 2 M aqueous sodium carbonate. The mixture was extracted with chloroform; the combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 5-(4-chlorobutyl)-1-ethyl-1*H*-pyrazole-3-carboxylate as a yellow oil that was used without purification.

Part B

Potassium acetate (92.6 g, 943 mmol), sodium iodide (7.0 g, 47 mmol), and *N,N*-dimethylformamide (DMF) (943 mL) were added to the material from Part A, and the reaction was heated at 90 °C for four hours under a nitrogen atmosphere and allowed to cool to ambient temperature. Water was added, and the resulting mixture was extracted with diethyl ether. The combined extracts were washed with water (3 x), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 5-(4-acetoxybutyl)-1-ethyl-1*H*-pyrazole-3-carboxylate, which was used without purification.

Part C

A solution of the material from Part B in methanol (150 mL) was treated with ammonium hydroxide (150 mL) according to a modification of the method described in Part D of Examples 1-4. The reaction was heated overnight at 125 °C and allowed to cool to ambient temperature. The methanol and some water were removed under reduced pressure, and the remaining solution was extracted with chloroform. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 18.0 g of 1-ethyl-5-(4-hydroxybutyl)-1*H*-pyrazole-3-carboxamide as a dark oil that was used without purification.

Part D

A modification of the method described in Part E of Examples 1-4 was used to treat 1-ethyl-5-(4-hydroxybutyl)-1*H*-pyrazole-3-carboxamide (18.2 g, 86.1 mmol) with phosphorous oxychloride (60 mL). The reaction was heated for three hours before cooling to 0 °C and pouring into ice water. The mixture was adjusted to pH 12 with the addition of 2 N aqueous sodium carbonate and extracted with chloroform. The combined extracts were passed through a layer of silica gel (eluting first with chloroform and then with 1:1 hexane/ethyl acetate to provide 10.8 g of 5-(4-chlorobutyl)-1-ethyl-1*H*-pyrazole-3-carbonitrile as a dark oil.

Part E

5-(4-Chlorobutyl)-1-ethyl-1*H*-pyrazole-3-carbonitrile (10.8 g, 51.0 mmol) was treated with potassium acetate (10.0 g, 102 mmol) and bromine (2.9 mL, 56 mmol) in acetic acid (102 mL), and the reaction was stirred overnight at ambient temperature. The acetic acid was removed under reduced pressure, and the residue was partitioned between

water and chloroform. The mixture was adjusted to pH 10 with the addition of 2 N aqueous sodium carbonate. The aqueous layer was extracted with chloroform, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by chromatography on a HORIZON HPFC system (eluting with hexanes/ethyl acetate in a gradient from 95:5 to 50:50) to provide 4-bromo-5-(4-chlorobutyl)-1-ethyl-1*H*-pyrazole-3-carbonitrile.

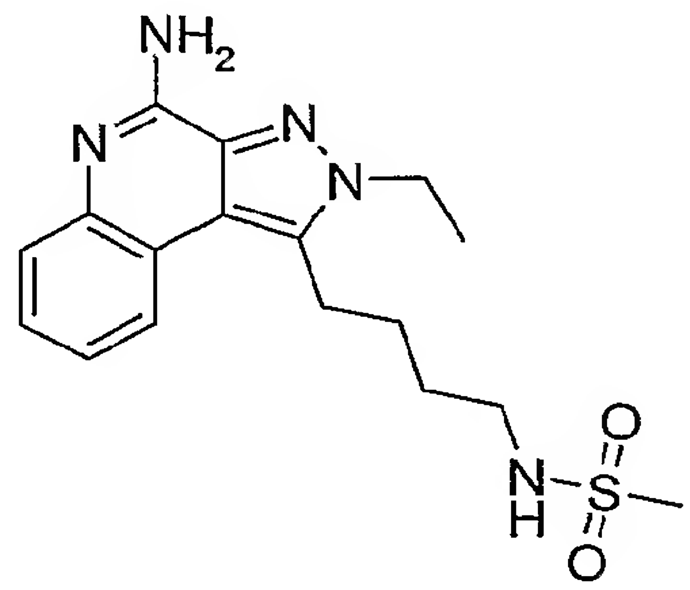
Part F

2-Aminophenylboronic acid hydrochloride (1.88 g, 10.8 mmol), potassium phosphate (6.9 g, 32 mmol), tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (186 mg, 0.18 mmol), and bis[(2-diphenylphosphino)phenyl]ether (116 mg, 0.217 mmol) were added to a solution of 4-bromo-5-(4-chlorobutyl)-1-ethyl-1*H*-pyrazole-3-carbonitrile (2.1 g, 7.2 mmol) in toluene (45 mL). Nitrogen was bubbled through the reaction mixture, and then the reaction was heated at 110 °C for 48 hours. The mixture was filtered through a layer of silica gel (eluting with 3:2 chloroform/methanol). The filtrate was concentrated under reduced pressure and dissolved in ethanol (36 mL). Hydrogen chloride (5.4 mL of a 4 M solution in ethanol) was added to the resulting solution, and the reaction was heated at reflux for two hours and allowed to cool to ambient temperature. The solvent was removed under reduced pressure, and the residue was adjusted to pH 11 with the addition of 2 M aqueous sodium carbonate. The mixture was diluted with brine and extracted with chloroform. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with chloroform/CMA in a gradient from 100:0 to 70:30). The resulting dark semi-solid was recrystallized from acetonitrile to provide 175 mg of 1-(4-chlorobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a tan solid.

Anal. Calcd for $C_{16}H_{19}ClN_4$: C, 63.47; H, 6.32; N, 18.50. Found: C, 63.80; H, 6.58; N, 18.38.

Example 20

N-[4-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]methanesulfonamide



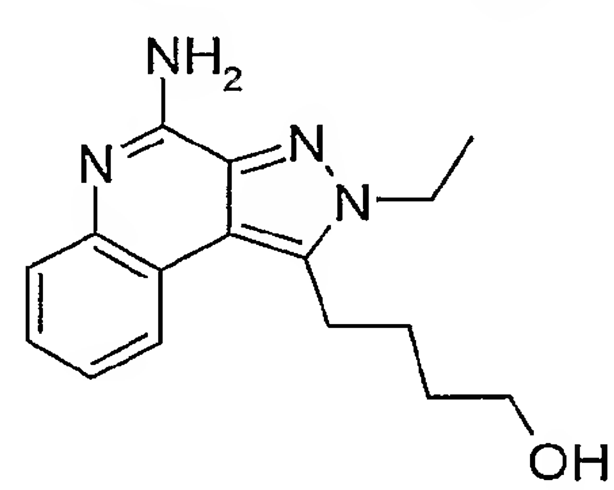
Methanesulfonamide (1.14 g, 12.0 mmol) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 480 mg, 12.0 mmol) in DMF (5 mL); the reaction was stirred for five minutes. 1-(4-Chlorobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (0.70 g, 2.4 mmol, prepared as described in Example 19) in DMF (2 mL) and sodium iodide (90 mg, 0.6 mmol) were sequentially added. The reaction was heated at 80 °C for one hour and 90 °C for three hours, allowed to cool to ambient temperature, and poured into ice water (70 mL). A precipitate was removed by filtration, and the filtrate was washed with diethyl ether. A precipitate formed in the aqueous layer over a period of 24 hours and was isolated by filtration and washed with water to provide 200 mg of *N*-[4-(4-amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]methanesulfonamide as tan crystals, mp 192-194 °C.

MS (APCI) *m/z* 362 $(M + H)^+$;

Anal. Calcd for $C_{17}H_{23}N_5O_2S$: C, 56.49; H, 6.41; N, 19.37. Found: C, 56.40; H, 6.56; N, 19.24.

Example 21

4-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butan-1-ol



Part A

Potassium acetate (1.69 g, 17.2 mmol), sodium iodide (255 mg, 1.7 mmol), and DMF (17 mL) were added to 4-bromo-5-(4-chlorobutyl)-1-ethyl-1*H*-pyrazole-3-

carbonitrile (1.0 g, 3.4 mmol, prepared as described in Parts A-E of Example 19), and the reaction was heated at 100 °C for two hours under a nitrogen atmosphere and allowed to cool to ambient temperature. Water was added, and the resulting mixture was extracted with diethyl ether. The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with hexanes/ethyl acetate in a gradient from 90:10 to 60:40) to provide 0.86 g of 4-(4-bromo-5-cyano-2-ethyl-2*H*-pyrazol-3-yl)butyl acetate.

Part B

Triphenylphosphine (21 mg, 0.082 mmol), 2-aminophenylboronic acid hydrochloride (710 mg, 4.1 mmol), 2 M aqueous sodium carbonate (4.1 mL), *n*-propanol (4.8 mL), and water (1 mL) were added to 4-(4-bromo-5-cyano-2-ethyl-2*H*-pyrazol-3-yl)butyl acetate (0.86 mg, 2.7 mmol), and the flask was evacuated and backfilled with nitrogen five times before the addition of palladium (II) acetate (6.0 g, 0.027 mmol). The reaction was evacuated and backfilled with nitrogen three more times and then heated overnight at 100 °C. An analysis by HPLC indicated that the reaction was incomplete. Additional triphenylphosphine (10 mg, 0.038 mmol), 2-aminophenylboronic acid hydrochloride (300 mg, 1.73 mmol), solid sodium carbonate (500 mg), and palladium (II) acetate (3.0 g, 0.013 mmol) were added at ambient temperature, and the reaction was heated at reflux for three hours and allowed to cool to ambient temperature. The reaction was diluted with brine and extracted with chloroform. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. Methanol (10 mL) and sodium methoxide (2.2 mL of a 47% solution in methanol) were added to the resulting dark oil. The reaction was heated at reflux for three hours, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was diluted with water and extracted with chloroform. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with chloroform/CMA in a gradient from 100:0 to 75:25) to provide an oil. The oil was crystallized from acetonitrile and recrystallized from acetonitrile to provide 250 mg of 4-

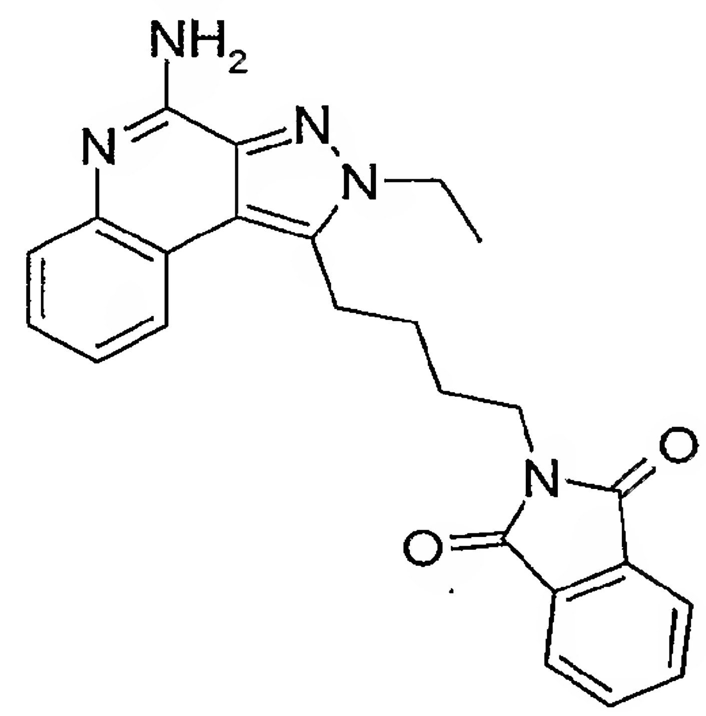
(4-amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butan-1-ol as gold-colored crystals, mp 159-160 °C.

MS (APCI) *m/z* 285 $(M + H)^+$;

Anal. Calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.32; H, 7.41; N, 19.80.

Example 22

2-[4-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]isoindole-1,3-dione



Part A

Potassium phthalimide (954 mg, 5.15 mmol), sodium iodide (130 mg, 0.86 mmol), and DMF (5 mL) were added to 4-bromo-5-(4-chlorobutyl)-1-ethyl-1*H*-pyrazole-3-carbonitrile (1.0 g, 3.4 mmol, prepared as described in Parts A-E of Example 19), and the reaction was heated at 100 °C for 45 minutes under a nitrogen atmosphere and allowed to cool to ambient temperature. Water (50 mL) was added, and the resulting mixture was stirred at 0 °C. A precipitate formed, was isolated by filtration, and was dissolved in chloroform. The resulting solution was dried over sodium sulfate, filtered, and concentrated under reduced pressure. An analysis by nuclear resonance spectroscopy (NMR) indicated that starting material was present. The solid was treated with potassium phthalimide (1.27 g, 6.88 mmol), sodium iodide (130 mg, 0.86 mmol), and DMF (5 mL) and heated at 90 °C for three hours. Water (50 mL) was added, and the resulting solid was isolated by filtration to provide 0.97 g of 4-bromo-1-ethyl-5-(4-phthalimidobutyl)-1*H*-pyrazole-3-carbonitrile as a gray, crystalline solid.

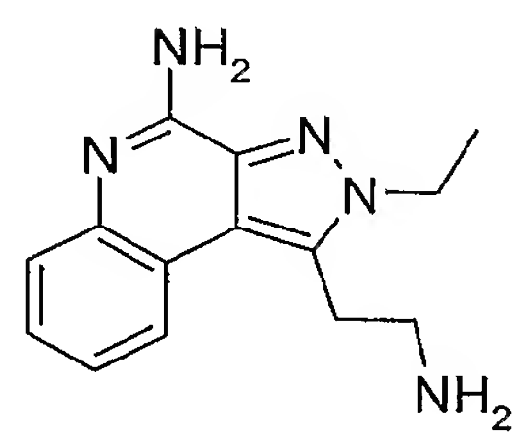
Part B

4-Bromo-1-ethyl-5-(4-phthalimidobutyl)-1*H*-pyrazole-3-carbonitrile (0.97 g, 2.4 mmol) was treated with 2-aminophenylboronic acid hydrochloride (839 mg, 4.84 mmol), potassium phosphate (2.56 g, 12.1 mmol), tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (124 mg, 0.12 mmol), and bis[(2-diphenylphosphino)phenyl]ether (75 mg, 0.14 mmol) according to the method described in Part F of Example 19. The reaction was heated for 24 hours. Following the purification and recrystallization, 0.157 g of 2-[4-(4-amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]isoindole-1,3-dione was obtained as brown crystals, mp 216-217 °C.

Anal. Calcd for $C_{24}H_{23}N_5O_2$: C, 69.72; H, 5.61; N, 16.94. Found: C, 69.47; H, 5.89; N, 16.94.

Example 23

1-(2-Aminoethyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride



Part A

4-Phthalimido-2-butanone was obtained from the literature procedure, Eriks *et al*, *J. Med. Chem.*, 1992, *35*, 3239-3246. Sodium *tert*-butoxide (20.75 g, 0.216 mol) was added over a period of 12 minutes to ethanol (160 mL) under a nitrogen atmosphere. When all solids had dissolved, diethyl oxalate (31.55 g, 0.216 mol) and a suspension of 4-phthalimido-2-butanone (46.9 g, 0.216 mol) were sequentially added. The reaction was stirred at ambient temperature for 2.5 hours. A precipitate was present and was isolated by filtration to provide 37.4 g of ethyl 2,4-dioxo-6-phthalimidohexanoate, sodium salt as a light orange solid.

Part B

A modification of the method described in Part A of Example 1 1 was followed. A solution of ethyl 2,4-dioxo-6-phthalimidohexanoate, sodium salt (37.64 g, 0.110 mol) in glacial acetic acid (160 L) was cooled to 10 °C before the addition of ethylhydrazine

oxalate (16.52 g, 0.110 mol). During the addition, the reaction temperature was maintained between 9 and 11 °C. The reaction was complete in two hours. The crude product, a reddish-orange oil, was treated with diethyl ether (150 mL) to form a solid, which was isolated by filtration to provide 26.5 g of ethyl 1-ethyl-5-(2-phthalimidoethyl)-1*H*-pyrazole-3-carboxylate as a tan solid.

Part C

A solution of ethyl 1-ethyl-5-(2-phthalimidoethyl)-1*H*-pyrazole-3-carboxylate (10.0 g, 29.3 mmol) in hydrochloric acid (20 mL of 1 M) and acetic acid (60 mL) was heated at 105 °C for 14.5 hours. An analysis by HPLC indicated the presence of starting material; the reaction was heated at 115 °C for three hours and cooled to ambient temperature. The reaction was poured into ice water (200 mL). A precipitate formed and was isolated by filtration, washed with water, and dried in the filter funnel for 1.5 hours to provide 7.64 g of white solid. Toluene (40 mL) and thionyl chloride (20 mL) were added to the white solid, and the mixture was heated at 115 °C for 40 minutes, cooled to ambient temperature, and concentrated under reduced pressure. Toluene was added and removed under reduced pressure. Dichloromethane (60 mL) was added to the residue, and the resulting solution was cooled to 0 °C. Concentrated ammonium hydroxide (20 mL) was added, a precipitate formed, and the reaction was stirred for five minutes. The mixture was concentrated under reduced pressure, and the resulting solid was washed with water twice and dried on the filter funnel. The solid was combined with material from another run and recrystallized from ethanol (45 mL/g) to provide 8.5 g of 1-ethyl-5-(2-phthalimidoethyl)-1*H*-pyrazole-3-carboxamide.

Part D

A solution of 1-ethyl-5-(2-phthalimidoethyl)-1*H*-pyrazole-3-carboxamide (8.5 g, 27.2 mmol) and thionyl chloride (20 mL) in toluene (40 mL) was heated at reflux for five hours, allowed to cool to ambient temperature, and concentrated under reduced pressure. The residue was dissolved in chloroform and made basic with the addition of 2 M sodium carbonate. The aqueous layer was separated at extracted with chloroform (4 x), and the combined organic fractions were washed with brine. The brine was extracted with chloroform (4 x). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product (8.08 g) was purified

by chromatography on a HORIZON HPFC system (65I cartridge, eluting with chloroform/CMA in a gradient from 100:0 to 80:20) to provide 7.73 g of 1-ethyl-5-(2-phthalimidoethyl)-1*H*-pyrazole-3-carbonitrile as a white solid.

Part E

Potassium acetate (3.9 g, 39.5 mmol) was added to a solution of 1-ethyl-5-(2-phthalimidoethyl)-1*H*-pyrazole-3-carbonitrile (7.73 g, 26.3 mmol) in acetic acid (37.5 mL) and dichloromethane (75 mL). Bromine (5.88 g, 36.8 mmol) was added, and the reaction was stirred for 14 hours. A precipitate was present. Saturated aqueous sodium hydrogensulfite was added, and the dichloromethane was removed under reduced pressure. Water (500 mL) was added with stirring, and the resulting solid was isolated by filtration, washed with water, and dried on the filter funnel to provide 4-bromo-1-ethyl-5-(2-phthalimidoethyl)-1*H*-pyrazole-3-carbonitrile.

Part F

Hydrazine hydrate (4.26 g, 85.1 mmol) was added to a solution of 4-bromo-1-ethyl-5-(2-phthalimidoethyl)-1*H*-pyrazole-3-carbonitrile (6.35 g, 17.0 mmol) in ethanol, and the solution was heated at reflux for one hour and cooled to ambient temperature. A precipitate formed and was isolated by filtration and washed with cold ethanol. The filtrate was concentrated under reduced pressure, and the resulting white solid was twice treated with toluene and concentrated under reduced pressure. The combined solids were dissolved in 1-methyl-2-pyrrolidinone (NMP) (30 mL), and di-*tert*-butyl dicarbonate (4.37 g, 20.0 mmol) was added. The reaction was stirred overnight, and additional di-*tert*-butyl dicarbonate (0.50 g, 2.3 mmol) was added. The reaction was stirred for 25 minutes and cooled to 0 °C. Water (350 mL) was added to form a precipitate, and the mixture was stirred for 30 minutes. The solid was isolated by filtration, washed with water, and purified by chromatography on a HORIZON HPFC system (65I cartridge, eluting with hexanes/ethyl acetate in a gradient from 60:40 to 40:60) to provide 5.73 g of [2-(4-bromo-5-cyano-2-ethyl-2*H*-pyrazol-3-yl)ethyl]*tert*-butyl carbamate as a white solid.

Part G

2-[(2,2-Dimethylpropanoyl)amino]phenylboronic acid (also known as 2-pivaloylaminobenzene)boronic acid) was prepared using the literature procedure of Rocca, P. *et al*, *Tetrahedron*, 1993, *49*, 49-64. The method described in Part G of Examples 1-4

was used to couple [2-(4-bromo-5-cyano-2-ethyl-2*H*-pyrazol-3-yl)ethyl]*tert*-butyl carbamate (5.50 g, 16.0 mmol) and (2-pivaloylaminobenzene)boronic acid (5.3 g, 24 mmol) in the presence of palladium (II) acetate (72 mg, 0.32 mmol), triphenylphosphine (252 mg, 0.96 mmol), and 2 M aqueous sodium carbonate (12 mL). After the reaction was heated for nine hours, additional palladium (II) acetate (72 mg, 0.32 mmol), triphenylphosphine (252 mg, 0.96 mmol), and 2-[(2,2-dimethylpropanoyl)amino]phenylboronic acid (1.8 g, 8.1 mmol) were added, and the reaction was heated for an additional 15 hours. The crude product was purified by chromatography on a HORIZON HPFC system (65I cartridge, eluting with hexanes/ethyl acetate in a gradient from 70:30 to 35:65) to provide 4.35 g of *tert*-butyl 2-(3-cyano-4-{2-[(2,2-dimethylpropanoyl)amino]phenyl}-1-ethyl-1*H*-pyrazol-5-yl)ethylcarbamate containing small amounts of [2-(4-bromo-5-cyano-2-ethyl-2*H*-pyrazol-3-yl)ethyl]*tert*-butyl carbamate and [2-(5-cyano-2-ethyl-2*H*-pyrazol-3-yl)ethyl]*tert*-butyl carbamate.

Part H

A solution of the material from Part G in ethanol (50 mL) was treated with sodium *tert*-butoxide (2 mmol) and heated at 100 °C under a nitrogen atmosphere for 3.5 hours. The reaction was allowed to cool to ambient temperature, and the ethanol was removed under reduced pressure. The residue was partitioned between chloroform and brine. The aqueous layer was separated and extracted with chloroform (4 x). The combined organic fractions were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with chloroform/CMA in a gradient from 95:5 to 60:40) to provide 1.71 g of 2-(4-amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)ethyl *tert*-butyl carbamate as a white solid containing a small amount of hexane.

Part I

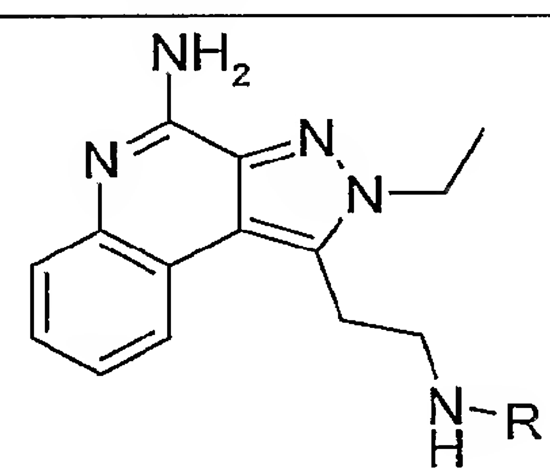
Hydrogen chloride (5 mL of a 4 M solution in ethanol) was added to a suspension of 2-(4-amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)ethyl *tert*-butyl carbamate (1.71 g) in ethanol (10 mL), and the reaction was heated at reflux for one hour and cooled to ambient temperature. A precipitate formed, and the reaction mixture was cooled to 0 °C. The solid was isolated by filtration and washed with diethyl ether to provide 1.521 g of 1-(2-aminoethyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride.

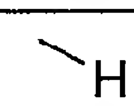
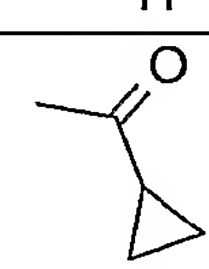
Examples 23-33

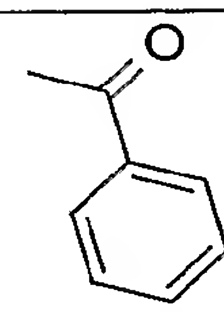
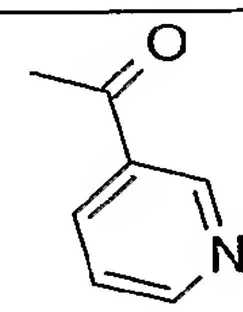
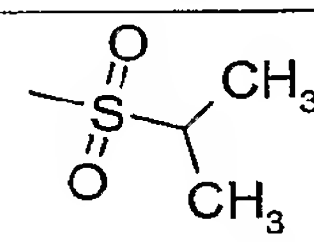
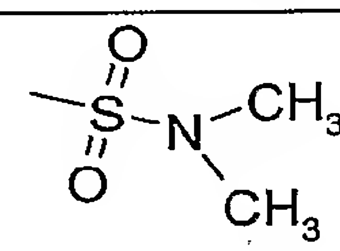
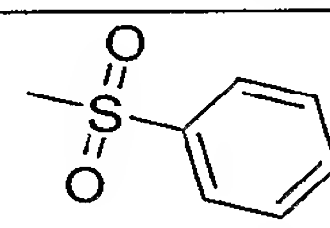
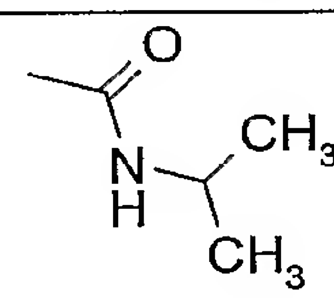
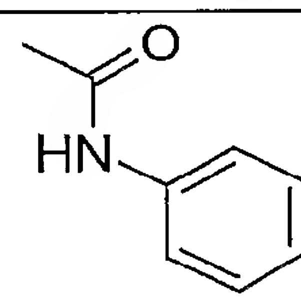
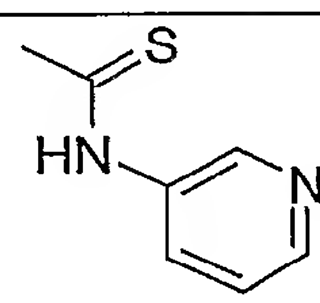
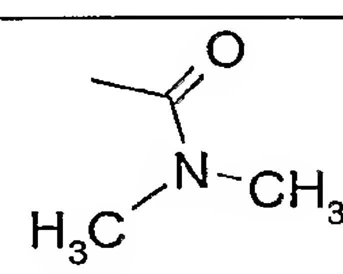
A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(2-aminoethyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride (32 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.068 mL, 0.4 mmol) in chloroform (1 mL). The test tubes were capped, shaken for four hours at ambient temperature, and allowed to stand overnight. Two drops of water were added to each test tube, and the solvent was removed by vacuum centrifugation.

The compounds were purified by preparative high-performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC/TOF-MS, and the appropriate fractions were combined and centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Column: Zorbax BonusRP, 21.2 x 50 millimeters (mm), 5 micron particle size; non-linear gradient elution from 5 to 95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 23-33

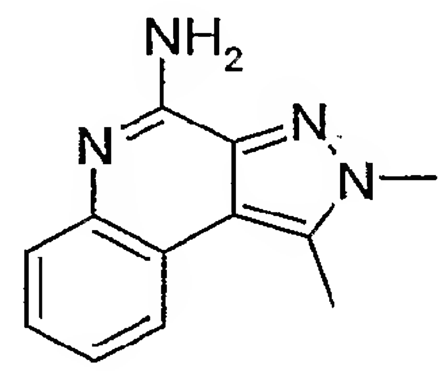


Example	Reagent	R	Measured Mass (M+H)
23	none		256.1570
24	Cyclopropanecarbonyl chloride		324.1846

25	Benzoyl chloride		360.1835
26	Nicotinoyl chloride hydrochloride		361.1784
27	Isopropylsulfonyl chloride		362.1665
28	Dimethylsulfamoyl chloride		363.1611
29	Benzenesulfonyl chloride		396.1493
30	Isopropyl isocyanate		341.2103
31	Phenyl isocyanate		375.1952
32	3-Pyridyl isothiocyanate		392.1692
33	*N,N*-Dimethylcarbamoyl chloride		327.1965

Example 34

1,2-Dimethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Triphenylphosphine (0.10 g, 0.45 mmol), 2-aminophenylboronic acid hydrochloride (3.89 g, 22.0 mmol), and 4-bromo-1,5-dimethyl-1*H*-pyrazole-3-carbonitrile (prepared as described in Parts A-C of Example 5, 3.00 g, 15.0 mmol) were placed in a flask. After 1-propanol was added (22 mL), the flask was placed under vacuum and back-filled with nitrogen three times. Palladium (II) acetate (30 mg, 0.15 mmol) was added, followed by aqueous sodium carbonate (22.5 mL of 2 M) and water (4.4 mL). The reaction was heated overnight under a nitrogen atmosphere at 100 °C. Additional 2-aminophenylboronic acid hydrochloride (1.0 g), palladium (II) acetate (approximately 10 mg), aqueous sodium carbonate (10 mL of 2 M), and water (5 mL) were added. The reaction was heated at 100 °C for 8 hours, then was allowed to cool to ambient temperature. The reaction mixture was partioned between dichloromethane and water. The organic layer was concentrated under reduced pressure and the crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-30% CMA in chloroform). The appropriate fractions were combined and concentrated under reduced pressure. The residue was dissolved in dichloromethane and concentrated under reduced pressure, which resulted in the formation of a solid. Hexanes were added to the solid, which was isolated by filtration and crystallized from acetonitrile to yield 0.637 g of 1,2-dimethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as white needles, mp >250 °C.

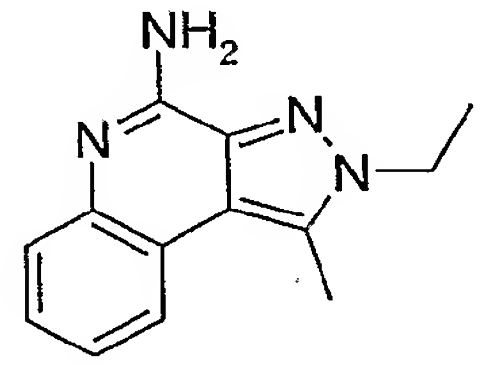
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, J = 7.8 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.60 (br s, 2H), 4.07 (s, 3H), 2.80 (s, 3H);

MS (APCI) *m/z* 213 $(M + H)^+$;

Anal. calcd for $C_{12}H_{12}N_4$•0.19 H_2O: C, 66.83; H, 5.79; N, 25.98. Found: C, 66.47; H, 5.64; N, 26.02.

Example 35

2-Ethyl-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Ethylhydrazine oxalate (23.7 g, 158 mmol) was added slowly to an 11 °C solution of ethyl acetopyruvate (50.0 g, 316 mmol) in ethanol so that the internal temperature did not exceed 14 °C. The reaction was allowed to warm to ambient temperature and was stirred overnight. The reaction was concentrated under reduced pressure and 2 M sodium carbonate was added to adjust the mixture to pH 9. The mixture was transferred to a separatory funnel. The aqueous phase was extracted with methyl *tert*-butyl ether (3 x 600 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 28.94 g of ethyl 1-ethyl-5-methyl-1*H*-pyrazole-3-carboxylate as an orange oil that was used without purification in the next reaction.

Part B

A mixture of the material prepared in Part A (28.94 g) and concentrated ammonium hydroxide (275 mL) was heated at 125 °C for 2 days in a pressure vessel. A precipitate formed and was isolated by filtration but was found to contain a mixture of material. The filtrate was stirred at 0 °C for 30 minutes and a white solid formed. The solid was isolated, washed with water, and dried to yield 10.22 g of 1-ethyl-5-methyl-1*H*-pyrazole-3-carboxamide as a white solid.

Part C

1-Ethyl-5-methyl-1*H*-pyrazole-3-carboxamide (10.2 g, 66.7 mmol) was treated with phosphorus oxychloride (41 mL) according to the method described in Part C of Example 8. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 1-21% ethyl acetate/hexanes followed by 2-25% CMA in chloroform). The appropriate fractions were combined and concentrated under

reduced pressure to yield 8.17 g of 1-ethyl-5-methyl-1*H*-pyrazole-3-carbonitrile as clear colorless crystals.

Part D

1-Ethyl-5-methyl-1*H*-pyrazole-3-carbonitrile (2.98 g, 22.0 mmol) was treated with potassium acetate (4.93 g, 31.0 mmol) and bromine (3.87 g, 24.0 mmol) in glacial acetic acid (43 mL) according to the general method described in Part F of Examples 1-4. Methyl *tert*-butyl ether was used instead of dichloromethane in the extraction during the work-up. The organic layers were combined and concentrated under reduced pressure to yield 4-bromo-1-ethyl-5-methyl-1*H*-pyrazole-3-carbonitrile as a white solid.

Anal. calcd for $C_7H_8BrN_3$: C, 39.28; H, 3.77; N, 19.63. Found: C, 39.30; H, 3.60; N, 19.77.

Part E

4-Bromo-1-ethyl-5-methyl-1*H*-pyrazole-3-carbonitrile (3.00 g, 14.0 mmol) was treated with triphenylphosphine (0.10 g, 0.42 mmol), 2-aminophenylboronic acid hydrochloride (3.64 g, 21.0 mmol), 1-propanol (22 mL), palladium (II) acetate (30 mg, 0.14 mmol), 2 M aqueous sodium carbonate (22.5 mL, 45 mmol), and water (4.4 mL) according to the general procedure described in Example 34. The reaction time was approximately 18 hours and no additional reagents were added. The crude product mixture was used in the next step without purification.

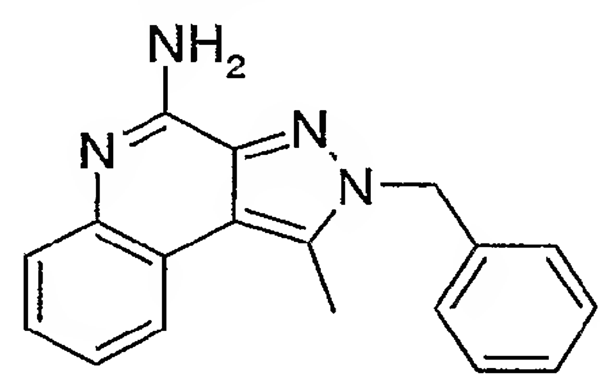
Part F

A solution of ethanolic HCl, generated from the addition of acetyl chloride (1.65 g, 21.0 mmol) to ethanol (21 mL), was added to the material from Part E according to a modification of the method described in Part G of Example 10. The reaction was heated at reflux and then heated at 81 °C overnight. The reaction mixture was allowed to cool to ambient temperature and a white solid was isolated by filtration and stirred in 2 M aqueous sodium carbonate. The mixture was transferred to a separatory funnel where it was extracted with chloroform twice. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting light brown solid was recrystallized from acetonitrile and isolated to yield 0.564 g of 2-ethyl-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as an off white powder, mp 217.0 – 218.0 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.01 (dd, J = 7.8, 1.2 Hz, 1H), 7.51 (dd, J = 8.1, 1.1 Hz, 1H), 7.34 (td, J = 7.6, 1.5 Hz, 1H), 7.21 (td, J = 7.5, 1.3 Hz, 1H), 6.65 (br s, 2H), 4.43 (q, J = 7.2 Hz, 2H), 2.82 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H);
MS (APCI) m/z 227 $(M + H)^+$;
Anal. calcd for $C_{13}H_{14}N_4$: C,69.00; H,6.24; N, 24.76. Found: C, 68.69; H, 6.21; N, 24.81.

Example 36

2-Benzyl-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Benzylhydrazine dihydrochloride (123.3 g, 0.632 mol) was added in batches to a 12 °C solution of ethyl acetopyruvate (100.0 g, 0.632 mol) and potassium acetate (155.1 g, 1.58 mol) in glacial acetic acid (1.044 L) so that the internal temperature did not exceed 16 °C. The cooling bath was removed and the reaction was allowed to stir overnight at ambient temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure to yield an orange oil to which 2 M aqueous sodium carbonate was added until pH 9 was reached. The mixture was extracted with methyl *tert*-butyl ether (3 x 1 L). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to yield 102.5 g of slightly impure ethyl 1-benzyl-5-methyl-1*H*-pyrazole-3-carboxylate.

Part B

A mixture of ethyl 1-benzyl-5-methyl-1*H*-pyrazole-3-carboxylate (57.57 g, 0.236 mol), concentrated ammonium hydroxide (114 mL), and methanol (114 mL) was heated at 125 °C for 39 hours in a pressure vessel. After cooling to ambient temperature, the vessel was placed in an ice bath and the reaction solution was stirred for 30 minutes until a precipitate formed. The precipitate was isolated by filtration and washed with water to yield 28.22 g of 1-benzyl-5-methyl-1*H*-pyrazole-3-carboxamide.

Part C

1-Benzyl-5-methyl-1*H*-pyrazole-3-carboxamide (28.22 g, 0.131 mol) was treated with phosphorus oxychloride (112 mL) according to the general method described in Part C of Example 8. The mixture was heated for 3 hours at 90 °C. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 1-25% ethyl acetate in hexanes). The appropriate fractions were combined, dried over magnesium sulfate, and concentrated under reduced pressure to yield 3.38 g of 1-benzyl-5-methyl-1*H*-pyrazole-3-carbonitrile as a white solid.

Part D

1-Benzyl-5-methyl-1*H*-pyrazole-3-carbonitrile (3.38 g, 17.1 mmol) was treated with potassium acetate (2.35 g, 24.0 mmol) and bromine (3.01 g, 18.9 mmol) in glacial acetic acid (48 mL) according to the method described in Part F of Examples 1-4. After the 2 M aqueous sodium carbonate was added in the work-up, a white solid was isolated by filtration and washed with water to yield 4.49 g of 1-benzyl-4-bromo-5-methyl-1*H*-pyrazole-3-carbonitrile.

Anal. calcd for $C_{12}H_{10}BrN_3$: C, 52.20; H, 3.65; N, 15.22. Found: C, 51.98; H, 3.45; N, 15.27.

Part E

1-Benzyl-4-bromo-5-methyl-1*H*-pyrazole-3-carbonitrile (3.00 g, 10.9 mmol) was treated with triphenylphosphine (85 mg, 0.32 mmol), 2-[(2,2-dimethylpropanoyl)amino]phenylboronic acid (prepared as described in Part G of Example 23, 2.15 g, 16.3 mmol), 1-propanol (22 mL), palladium (II) acetate (24 mg, 0.11 mmol), aqueous sodium carbonate (6.5 mL of 2 M, 13 mmol), and water (4.4 mL) according to the general procedure described in Example 34. The reaction time was approximately 16 hours and no additional reagents were added. The reaction was allowed to cool to ambient temperature and methyl *tert*-butyl ether (25 mL) was added. After the mixture was stirred for about 10 minutes, the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a brown oil. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution 1-30% ethyl acetate in hexanes). The appropriate fractions were combined, dried over magnesium sulfate, filtered, and concentrated to yield 2.40 g of *N*-[2-(1-benzyl-3-cyano-5-

methyl-1*H*-pyrazol-4-yl)phenyl]-2,2-dimethylpropanamide as an oil that solidified upon standing at ambient temperature.

Part F

A solution of *N*-[2-(1-benzyl-3-cyano-5-methyl-1*H*-pyrazol-4-yl)phenyl]-2,2-dimethylpropanamide (2.40 g, 6.44 mmol) and sodium *tert*-butoxide (0.743 g, 7.73 mmol) in ethanol (28 mL) was heated at reflux for 1 day, then was allowed to cool to ambient temperature. A precipitate formed that was isolated by filtration and washed with water followed by water/ethanol (8:1) to provide 1.33 g of 2-benzyl-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white powder, mp >250 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.00 (dd, J = 7.9, 1.2 Hz, 1H), 7.51 (dd, J = 8.1, 1.1 Hz, 1H), 7.38-7.28 (m, 4H), 7.21-7.15 (m, 3H), 6.70 (br s, 2H), 5.70 (br s, 2H), 2.77 (s, 3H); MS (APCI) *m/z* 289 (M + H)$^+$;

Anal. calcd for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.80; H, 5.65; N, 19.55.

Examples 37-39

Part A

Diethyl oxalate and 4,4-dimethyl-2-pentanone were treated with sodium *tert*-butoxide in ethanol according to the procedure described in Part A of Examples 1-4. The product was isolated, washed with ethanol, and dried under vacuum to provide ethyl 4-hydroxy-6,6-dimethyl-2-oxohept-3-enoate, sodium salt as a white solid.

Part B

A hydrazine reagent from the table below (1 equivalent) was added slowly to a 11 °C stirred 0.65 M solution of ethyl 4-hydroxy-6,6-dimethyl-2-oxohept-3-enoate, sodium salt (1 equivalent) in glacial acetic acid such that the internal temperature did not exceed 14 °C. In Example 38, the acetic acid solution also contained potassium acetate (1.5 equivalents). When the addition was complete, the ice bath was removed and the reaction was allowed to stir overnight at ambient temperature. The solution was concentrated under reduced pressure. To the resulting oil was added 2 M aqueous sodium carbonate the mixture reached pH 9. The mixture was extracted with methyl *tert*-butyl ether three times.

The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to yield an oil.

Part C

The material from Part B (37.8–45.4 g, 169–190 mmol) in a 1:1 mixture of concentrated ammonium hydroxide/methanol (150-200 mL) was heated at 125 °C for 24 hours in a pressure vessel. After cooling to ambient temperature, the vessel was placed in an ice bath. The reaction mixture was stirred for 30 minutes and a precipitate formed. The precipitate was isolated by filtration and washed with water to yield a carboxamide.

Part D

A mixture of the carboxamide (7.05-13.27 g, 29.7-63.5 mmol) and phosphorous oxychloride (28-52 mL) was heated at 90 °C for 3 hours. The mixture was allowed to cool to ambient temperature and was poured onto ice water (360-680 mL). Additional ice was added. Concentrated ammonium hydroxide was added to adjust the mixture to pH 8-9. The mixture was extracted with methyl *tert*-butyl ether. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide an oil.

Part E

Potassium acetate (1.4 equivalents) followed by bromine (1.1 equivalents) were added to a 0.4 M solution of the material from Part D in acetic acid. The reaction was stirred for 18-72 hours at ambient temperature. Saturated aqueous sodium hydrogensulfite was added to reduce the residual bromine. The mixture was concentrated under reduced pressure and 2 M aqueous sodium bicarbonate was added to adjust the mixture to pH 9. A white solid formed and was isolated by filtration and washed with water to provide a 1-alkyl-4-bromo-5-(2,2-dimethylpropyl)-1*H*-pyrazole-3-carbonitrile.

Example 38: 4-Bromo-1-ethyl-5-(2,2-dimethylpropyl)-1*H*-pyrazole-3-carbonitrile was obtained as a white solid.

Anal. calcd for $C_{11}H_{16}BrN_3$: C, 48.90; H, 5.97; N, 15.55. Found: C, 48.88; H, 6.26; N, 15.52.

Example 39: 4-Bromo-1-butyl-5-(2,2-dimethylpropyl)-1*H*-pyrazole-3-carbonitrile was obtained as a white solid.

Anal. calcd for $C_{13}H_{20}BrN_3$: C, 52.36; H, 6.76; N, 14.09. Found: C, 52.06; H, 7.02; N, 13.78.

Part F

Triphenylphosphine (0.03 equivalent), 2-aminophenylboronic acid hydrochloride (1.5-2.0 equivalents), and the material from Part E (1 equivalent) were placed in a flask. After 1-propanol was added (so that the concentration of material from Part E was 0.55 M), the flask was placed under vacuum and back-filled with nitrogen three times. Palladium (II) acetate (0.01 equivalent) was added, followed by 2 M aqueous sodium carbonate (3 equivalents) and water (1/5 of the amount of 1-propanol). The reaction was heated overnight under a nitrogen atmosphere at 100 °C. The reaction was allowed to cool to ambient temperature and methyl *tert*-butyl ether was added. After the mixture was stirred for about 10 minutes, the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a brown oil. In Examples 37 and 38 the oil was used directictly in the next step. In Example 39, the crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-20% ethyl acetate in hexanes). The appropriate fractions were combined, dried over magnesium sulfate, filtered, and concentrated to yield an oil.

Part G

The oil prepared in Part F was converted into a 2-alkyl-1-(2,2-dimethylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine using the general procedure described in Part H of Examples 1-4.

Example 37: 2-Methyl-1-(2,2-dimethylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was isolated as an off-white powder, mp 254.0 – 255.0 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.16 (dd, J = 7.9, 1.1 Hz, 1H), 7.50 (dd, J = 8.1, 1.2 Hz, 1H), 7.31 (td, J = 7.1, 1.3 Hz, 1H), 7.17 (td, J = 8.1, 1.4 Hz, 1H), 6.67 (br s, 2H), 4.10 (s, 3H), 3.25 (s, 2H), 1.02 (s, 9H);

MS (APCI) m/z 269 $(M + H)^+$;

Anal. calcd for $C_{16}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.37; H, 7.50; N, 21.04.

Example 38: No chromatographic purification was necessary. After crystallization from acetonitrile, 2-ethyl-1-(2,2-dimethylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was isolated as a off-white needles, mp 239.8 – 240.2 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (dd, J = 8.0, 1.2 Hz, 1H), 7.48 (dd, J = 8.1, 1.3 Hz, 1H), 7.30 (dt, J = 7.1, 1.4 Hz, 1H), 7.16 (dt, J = 8.0, 1.4 Hz, 1H), 6.61 (br s, 2H), 4.43 (q, J = 7.1 Hz, 2H), 3.26 (br s, 2H), 1.46 (t, J = 7.1 Hz, 3H), 1.01 (s, 9H).

Anal. calcd for $C_{17}H_{22}N_4$: C, 72.31; H, 7.85; N, 19.84. Found: C, 71.94; H, 8.01; N, 19.80.

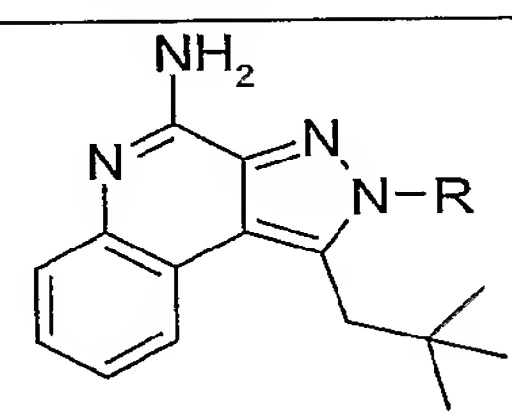
Example 39: No chromatography or crystallization steps necessary. 2-Butyl-1-(2,2-dimethylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was isolated as a white powder, mp 163.0 – 164.0 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.15 (dd, J = 7.9, 0.7 Hz, 1H), 7.49 (dd, J = 8.1, 1.0 Hz, 1H), 7.30 (td, J = 8.1, 1.1 Hz, 1H), 7.16 (td, J = 8.0, 1.1 Hz, 1H), 6.62 (br s, 2H), 4.39 (t, J = 6.9 Hz, 2H), 3.27 (br s, 2H), 1.87 (pentet, J = 7.2 Hz, 2H), 1.28 (sextet, J = 7.5 Hz, 2H), 1.00 (s, 9H), 0.89 (t, J = 7.3 Hz, 3H);

MS (APCI) m/z 311 $(M + H)^+$;

Anal. calcd for $C_{19}H_{26}N_4$: C, 73.51; H, 8.44; N, 18.05. Found: C, 73.34; H, 8.21; N, 18.19.

Examples 37-39



Example	Hydrazine reagent in Part B	R
37	Methylhydrazine	$-CH_3$
38	Ethylhydrazine oxalate	$-CH_2CH_3$
39	Butylhydrazine oxalate	$-CH_2CH_2CH_2CH_3$

Examples 40-42

Part A

Diethyl oxalate and benzylacetone were treated with sodium *tert*-butoxide in ethanol according to the procedure described in Part A of Examples 1-4. The reaction solution was stirred for 90 minutes and a precipitate formed. The precipitate was isolated to provide ethyl-4-hydroxy-2-oxo-6-phenylhex-3-enoate, sodium salt as a white solid.

Part B

A hydrazine reagent from the table below (1 equivalent) was added to a solution of ethyl-4-hydroxy-2-oxo-6-phenylhex-3-enoate, sodium salt (1 equivalent) in glacial acetic acid according to the procedure described in Part B of Examples 37-39. The product was isolated as an oil.

Part C

The material from Part B was treated with a 1:1 mixture of concentrated ammonium hydroxide/methanol (150-200 mL) according to the procedure described in Part C of Examples 37-39 to yield a carboxamide. Example 40 was heated for 2 days, Example 41 was heated for 18 hours, and Example 42 was heated for 1 day.

Part D

The carboxamide from Part C was treated with phosphorous oxychloride according to the procedure described in Part D of Examples 37-39 to yield the nitrile as an oil.

Part E

The material from Part D was brominated according to the procedure described in Part E of Examples 37-39. During the work-up in Examples 41 and 42, the mixture at pH 9 was extracted with methyl *tert*-butyl ether twice. The organic layers were combined, dried over magnesium sulfate, and concentrated to give a brown oil.

Part F

The material from Part E (3.00 g) was treated with triphenylphosphine (0.03 equivalent), 2-[(2,2-dimethylpropanoyl)amino]phenylboronic acid (prepared as described in Part G of Example 23, 1.5 equivalents), 1-propanol (22 mL), palladium (II) acetate (0.01 equivalent), 2 M aqueous sodium carbonate (1.2 equivalents), and water (4.4 mL) according to the general procedure described in Examples 37-39. The crude product was

purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-25% ethyl acetate in hexanes) to yield an oil.

Part G

To a 0.2 M solution of the material from Part F in ethanol was added sodium *tert*-butoxide (1.2 equivalents). The solution was heated at reflux for 1 day, then was allowed to cool to ambient temperature. A precipitate formed that was isolated by filtration and washed with a small amount of water and ethanol. The solid was dried at 70 °C in a vacuum oven overnight to provide the product products listed below.

Example 40: 2-Methyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was isolated as pale yellow powder, mp 210.5 — 212.5 °C.

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 7.97 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.37-7.15 (m, 7H), 6.67 (br s, 2H), 3.77 (s, 3H), 3.51 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.5 Hz, 2H);

MS (APCI) *m/z* 303 $(M + H)^+$;

Anal. calcd for $C_{19}H_{18}N_4 \cdot 0.17\ H_2O$: C, 74.71; H, 6.05; N, 18.34. Found: C, 74.40; H, 5.83; N, 18.31.

Example 41: 2-Ethyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was isolated as a white powder, mp 179.0 - 181.0 °C.

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 7.97 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.37-7.20 (m, 7H), 6.65 (br s, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.53 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 2H), 1.32 (t, *J* = 7.2 Hz, 3H);

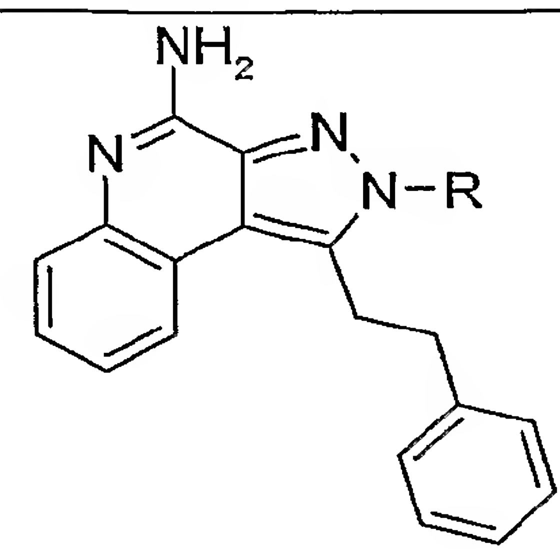
Anal. calcd for $C_{20}H_{20}N_4$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.71; H, 6.75; N, 17.82.

Example 42: 1-(2-Phenylethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was isolated as a white powder, mp 175.0 – 176.0 °C.

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 7.97 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.54 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.37-7.20 (m, 7H), 6.65 (br s, 2H), 4.07 (t, *J* = 7.2 Hz, 2H), 3.53 (t, *J* = 7.4 Hz, 2H), 3.03 (t, *J* = 7.7 Hz, 2H), 1.75 (sextet, *J* = 7.3 Hz, 2H), 0.85 (t, *J* = 7.3 Hz, 3H);

Anal. calcd for $C_{21}H_{22}N_4$: C, 76.33; H, 6.71; N, 16.96. Found: C, 76.10; H, 6.69; N, 16.90.

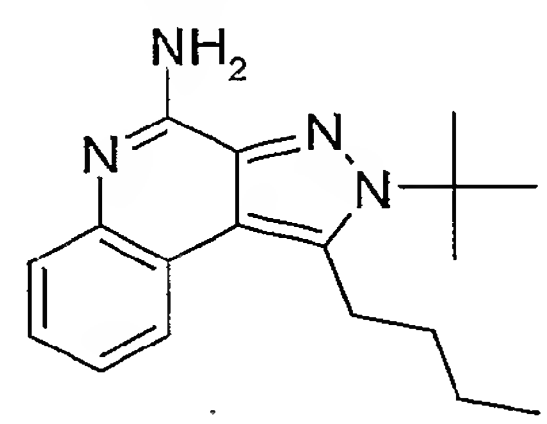
Examples 40-42



Example	Hydrazine reagent in Part B	R
40	Methylhydrazine	$-CH_3$
41	Ethylhydrazine oxalate	$-CH_2CH_3$
42	Propylhydrazine oxalate	$-CH_2CH_2CH_3$

Example 43

1-Butyl-2-*tert*-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Diethyl oxalate and 2-hexanone were treated with sodium *tert*-butoxide in ethanol according to the procedure described in Part A of Examples 1-4. The reaction solution was stirred for 90 minutes and a precipitate formed. The precipitate was isolated to provide 1-ethoxy-1,2-dioxooct-3-en-4-olate, sodium salt as a white solid.

Part B

1-Ethoxy-1,2-dioxooct-3-en-4-olate, sodium salt (332.8 g, 1.50 mol) was treated with *tert*-butylhydrazine hydrochloride (186.6 g, 1.50 mol) according to the procedure described in Part B of Examples 37-39 to yield ethyl 5-butyl-1-*tert*-butyl-1*H*-pyrazole-3-carboxylate as a brown oil.

Part C

Ethyl 5-butyl-1-*tert*-butyl-1*H*-pyrazole-3-carboxylate (60 g, 0.24 mol) in a 1:1 mixture of concentrated ammonium hydroxide/methanol (238 mL) was heated at 125 °C

for 37 hours in a pressure vessel. After cooling to ambient temperature, the vessel was placed in an ice bath. The reaction mixture was stirred for 30 minutes, then was concentrated under reduced pressure to a brown oil. The oil was dissolved in dichloromethane and the solution was washed with water and brine. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a wet brown solid. Hexanes were added, the mixture was stirred, and 18.67 g of 5-butyl-1-*tert*-butyl-1*H*-pyrazole-3-carboxamide was isolated by filtration as an off-white solid.

Part D

A solution of trifluoroacetic anhydride (13.5 mL, 95.4 mmol) in dichloromethane (84 mL) was added over 15 minutes to a 0 °C solution of 5-butyl-1-*tert*-butyl-1*H*-pyrazole-3-carboxamide (18.7 g, 86.7 mmol) and triethylamine (36.3 mL, 260 mmol) in dichloromethane (167 mL). The reaction was allowed to stir for 10 minutes before the ice bath was removed. The reaction was stirred at ambient temperature for 1 hour and then 2 M aqueous sodium carbonate was added. The mixture was transferred to a separatory funnel and was extracted with dichloromethane three times. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, eluted with 20% ethyl acetate in hexanes). The appropriate fractions were combined, dried over magnesium sulfate, and concentrated under reduced pressure to yield 11.00 g of 5-butyl-1-*tert*-butyl-1*H*-pyrazole-3-carbonitrile as an orange oil.

Part E

5-Butyl-1-*tert*-butyl-1*H*-pyrazole-3-carbonitrile (11.00 g, 53.6 mmol) was converted into 4-bromo-5-butyl-1-*tert*-butyl-1*H*-pyrazole-3-carbonitrile using the procedure described in Part E of Examples 37-39.

Part F

4-Bromo-5-butyl-1-*tert*-butyl-1*H*-pyrazole-3-carbonitrile (3.0 g, 10.6 mmol) was treated with triphenylphosphine (0.085 g, 0.32 mmol), 2-[(2,2-dimethylpropanoyl)amino]phenylboronic acid (prepared as described in Part G of Example 23, 2.41 g, 15.8 mmol), 1-propanol (22 mL), palladium (II) acetate (0.024 g, 0.11 mmol), 2 M aqueous sodium carbonate (6.5 mL, 13.0 mmol), and water (4.4 mL) according to the general procedure described in Examples 37-39. The crude product was purified by

chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-25% ethyl acetate in hexanes) to yield 1.63 g of *N*-[2-(5-butyl-1-*tert*-butyl-3-cyano-1*H*-pyrazol-4-yl)phenyl]-2,2-dimethylpropanamide as an oil.

Part G

To a solution of *N*-[2-(5-butyl-1-*tert*-butyl-3-cyano-1*H*-pyrazol-4-yl)phenyl]-2,2-dimethylpropanamide (1.63 g, 4.28 mmol) in ethanol was added sodium *tert*-butoxide (0.494 g, 5.14 mmol). The solution was heated at reflux for 1 day, then was allowed to cool to ambient temperature. A precipitate formed that was isolated by filtration and washed with a small amount of water (24 mL) and ethanol (3 mL) to yield 0.4667 g of 1-butyl-2-*tert*-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as off-white crystals, mp 222.0 – 223.0 °C.

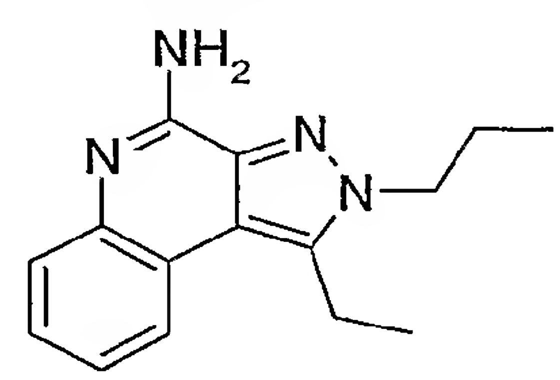
^{1}H NMR (300 MHz, DMSO-d_6 at 46 °C) δ 7.83 (dd, J = 7.9, 1.1 Hz, 1H), 7.50 (dd, J = 8.1, 1.3 Hz, 1H), 7.34 (td, J = 7.2, 1.4 Hz, 1H), 7.23 (td, J = 7.9, 1.4 Hz, 1H), 6.52 (br s, 2H), 3.39-3.34 (m, 2H), 1.76 (s, 9H), 1.72-1.56 (m, 4H), 1.01 (t, J = 7.1 Hz, 3H);

MS (APCI) *m/z* 297 $(M + H)^+$;

Anal. calcd for $C_{18}H_{24}N_4$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.67; H, 8.29; N, 19.01.

Example 44

1-Ethyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A solution of ethyl 2,4-dioxohexanoate (~0.464 mol), prepared as described in Part A of Example 10, in glacial acetic acid (300 mL) was cooled to O °C. Hydrazine (8.91 g, 0.278 mol) was added dropwise. The reaction was allowed to warm to ambient temperature, stirred overnight, and concentrated under reduced pressure. The residue was adjusted to pH 10 with the addition of 2 M aqueous sodium carbonate. The mixture was extracted with chloroform (3 x 250 mL). The combined organic layers were dried over

sodium sulfate, filtered, and concentrated under reduced pressure to provide 27.0 g of ethyl 5-ethyl-1*H*-pyrazole-3-carboxylate, which was used without purification.

Part B

Propyl iodide (0.43 mL, 4.46 mmol) and a solution of sodium ethoxide in ethanol (21%, 0.95 g, 3.27 mmol) were added to a solution of ethyl 5-ethyl-1*H*-pyrazole-3-carboxylate (0.5 g, 2.97 mmol) in ethanol (5 mL) at ambient temperature. The reaction was stirred overnight, and additional propyl iodide (0.05 mL) and sodium ethoxide in ethanol (21%, 0.1 g) were added. After 3 hours, the solvent was removed under reduced pressure and the residue was partitioned between an aqueous sodium chloride solution and methyl *tert*-butyl ether. The aqueous phase was extracted with methyl *tert*-butyl ether twice. The organic phases were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield impure ethyl 5-ethyl-1-propyl-1*H*-pyrazole-3-carboxylate.

Part C

Ethyl 5-ethyl-1-propyl-1*H*-pyrazole-3-carboxylate (13.0 g, 62 mmol) in a 4:1 mixture of concentrated ammonium hydroxide/methanol (50 mL) was heated at 125 °C for 18 hours in a pressure vessel. After cooling to ambient temperature, the contents of the vessel were poured into a flask and a precipitate formed immediately. The precipitate was isolated by filtration to yield 5.02 g of analytically pure 5-ethyl-1-propyl-1*H*-pyrazole-3-carboxamide as off-white crystals, mp 105-106 °C. MS (APCI) *m/z* 182.1 $(M+H)^+$; Anal. calcd for $C_9H_{15}N_3O$: C, 59.64; H, 8.34; N, 23.19. Found: C, 59.59; H, 8.54; N, 23.39. An additional 0.50 g of product was obtained in the second crop from the filtrate.

Part D

5-Ethyl-1-propyl-1*H*-pyrazole-3-carboxamide (5.50 g, 30.35 mmol) was treated with phosphorous oxychloride (20 mL) according to the procedure described in Part D of Examples 37-39 to yield 4.89 g of 5-ethyl-1-propyl-1*H*-pyrazole-3-carbonitrile as an oil.

Part E

5-Ethyl-1-propyl-1*H*-pyrazole-3-carbonitrile (4.89 g, 30.0 mmol) was dissolved in glacial acetic acid (30 mL) and treated with potassium acetate (4.41 g, 44.9 mmol) and bromine (4.79 g, 30.0 mmol). During the slow addtion of bromine, an exotherm occurred and and ice bath was used to cool the reaction. After the addition of bromine was

complete, the reaction was allowed to warm to ambient temperature and stir for 5 hours. Saturated aqueous sodium hydrogensulfite was added to reduce the residual bromine. The mixture was concentrated under reduced pressure and 2 M aqueous sodium carbonate was added to adjust the mixture to pH 9. The mixture was extracted with chloroform (3 x 100 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to yield 6.12 g of 4-bromo-5-ethyl-1-propyl-1*H*-pyrazole-3-carbonitrile as a yellow oil.

Part F

A mixture of 4-bromo-5-ethyl-1-propyl-1*H*-pyrazole-3-carbonitrile (4.00 g, 16.5 mmol), 2-aminophenylboronic acid hydrochloride (4.30 g, 24.8 mmol), triphenylphosphine (0.26 g, 0.99 mmol), palladium (II) acetate (0.074 g, 0.33 mmol), 2 M aqueous sodium carbonate (24.8 mL, 49.5 mmol), 1-propanol (35 mL), and water (5 mL) was heated at reflux for 18 hours. Additional triphenylphosphine (0.26 g) and palladium (II) acetate (0.074 g) were added and the mixture was heated at reflux for 22 hours. The mixture was allowed to cool to ambient temperature and methyl *tert*-butyl ether (100 mL) was added. The mixture was transferred to a separatory funnel and the organic layer was isolated and washed with water and brine. The aqueous layers were combined and back-extracted with methyl *tert*-butyl ether (2 x 40 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to provide a red oil that was used in the next step without purification.

Part G

The oil prepared in Part F was converted into 1-ethyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine using the general procedure described in Part H of Examples 1-4. 1-Ethyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (0.34 g) was isolated an off-white solid, mp 219-220 °C.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 7.91 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.50 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.37-7.27 (m, 1H), 7.25-7.15 (m, 1H), 6.64 (br s, 2H), 4.34 (t, *J* = 7.2 Hz, 2H), 3.25 (q, *J* = 7.5 Hz, 2H), 1.92 (sextet, *J* = 7.3 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H);

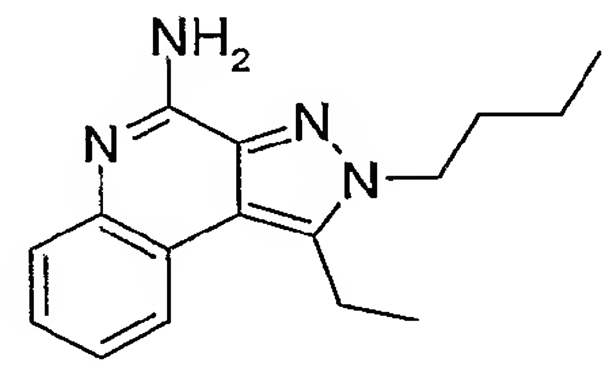
^{13}C-NMR (75 MHz, DMSO-d_6) δ 150.5, 143.7, 139.0, 135.5, 125.5, 121.6, 119.6, 116.0, 50.7, 23.6, 18.2, 13.1, 10.9.

MS (APCI) m/z 255.2 $(M+H)^+$;

Anal. calcd for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.49; H, 7.38; N, 22.12.

Example 45

2-Butyl-1-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A solution of ethyl 2,4-dioxohexanoate (approximately 60% pure, 45.0 g, 0.232 mol), prepared as described in Part A of Example 10, in glacial acetic acid (150 mL) was cooled to 0 °C. Butylhydrazine oxalate (25.0 g, 0.139 mol) was added slowly. The reaction was allowed to warm to ambient temperature, stirred overnight, and concentrated under reduced pressure. The residue was adjusted to pH 10 with the addition of 2 M aqueous sodium carbonate. The mixture was extracted with chloroform and an emulsion that contained solid material formed. The solid was isolated by filtration, and the filtrate was transferred to the separatory funnel. The organic layer was separated. The aqueous layer was extracted with chloroform three times. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide an oil that was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with CMA in chloroform) to yield 13.27 g of ethyl 5-ethyl-1-butyl-1*H*-pyrazole-3-carboxylate as a yellow oil.

Part B

Ethyl 5-ethyl-1-butyl-1*H*-pyrazole-3-carboxylate (13.27 g, 59.2 mmol) in concentrated ammonium hydroxide (50 mL) was heated at 125 °C for 14 hours in a pressure vessel. After the vessel was allowed to cool to ambient temperature, methanol (40 mL) was added and the vessel was heated at 125 °C for 1 day. After cooling to ambient temperature, the vessel was cooled in an ice bath and the product began to crystallize from the reaction mixture. Two crops of crystals were isolated to provide 5.50

g of 5-ethyl-1-butyl-1*H*-pyrazole-3-carboxamide as off-white crystals, mp 60-61 °C. MS (APCI) *m/z* 196.1 $(M+H)^+$; Anal. calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.32; H, 9.04; N, 21.71.

Part C

5-Ethyl-1-butyl-1*H*-pyrazole-3-carboxamide (5.44 g, 27.9 mmol) was treated with phosphorous oxychloride (20 mL) according to the procedure described in Part D of Examples 37-39 to yield 5.20 g of an oil. Chloroform was used in place of methyl *tert*-butyl ether in the work-up.

Part D

Potassium acetate (4.11 g, 41.9 mmol) followed by bromine (4.46 g, 27.9 mmol) were added to a cooled solution of the material from Part C in acetic acid (35 mL). The reaction was stirred for 48 hours at ambient temperature. The solution was concentrated under reduced pressure and 2 M aqueous sodium bicarbonate was added to adjust the mixture to pH 9-10. The mixture was extracted with methyl *tert*-butyl ether (250 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 5.87 g of 4-bromo-1-butyl-5-ethyl-1*H*-pyrazole-3-carbonitrile as a yellow oil that was used in the next step without purification.

Part E

A flask containing a mixture of 4-bromo-1-butyl-5-ethyl-1*H*-pyrazole-3-carbonitrile (2.56 g, 10 mmol), 2-[(2,2-dimethylpropanoyl)amino]phenylboronic acid (2.87 g, 15 mmol), triphenylphosphine (0.079 g, 0.30 mmol), 2 M aqueous sodium carbonate (15 mL, 30 mmol), water (3 mL) and 1-propanol (20 mL) was placed under vacuum and back-filled with nitrogen three times. Palladium (II) acetate (0.023 g, 0.10 mmol) was added. Again, the flask was placed under vacuum and back-filled with nitrogen. The mixture was heated overnight under a nitrogen atmosphere at 100 °C. The reaction was allowed to cool to ambient temperature and methyl *tert*-butyl ether was added. After the mixture was stirred for about 10 minutes, the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield a brown oil. Hexanes were added to the brown oil, causing the formation of a tan solid that was isolated by filtration. The filtrate was concentrated to an oil that was purified by chromatography on a HORIZON HPFC system (silica gel, eluted with ethyl acetate/hexanes) to provide 0.45 g of *N*-[2-(5-

ethyl-1-butyl-3-cyano-1*H*-pyrazol-4-yl)phenyl]-2,2-dimethylpropanamide, which was used in the next step without further purification.

Part F

To a solution of *N*-[2-(5-ethyl-1-butyl-3-cyano-1*H*-pyrazol-4-yl)phenyl]-2,2-dimethylpropanamide (0.45 g, 1.28 mmol) in ethanol (8 mL) was added sodium ethoxide in ethanol (21 wt% solution in ethanol, 1.03 g, 3.19 mmol). The solution was heated at reflux overnight, then was allowed to cool to ambient temperature. The solvent was removed under reduced pressure and the residue was triturated with water. A precipitate formed that was isolated by filtration and washed with water, then was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-35% CMA in chloroform) to yield 0.14 g of 1-ethyl-2-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white crystalline solid, mp 215-216 °C.

^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 7.90 (dd, J = 7.8, 1.2 Hz, 1 H), 7.49 (dd, J = 8.1, 1.1 Hz, 1H), 7.37-7.27 (m, 1H), 7.24-7.16 (m, 1H), 6.63 (br s, 2H), 4.37 (t, J = 7.3 Hz, 2H), 3.25 (q, J = 7.5 Hz, 2H), 1.93-1.80 (m, 2H), 1.43-1.30 (m, 2H), 1.29 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H);

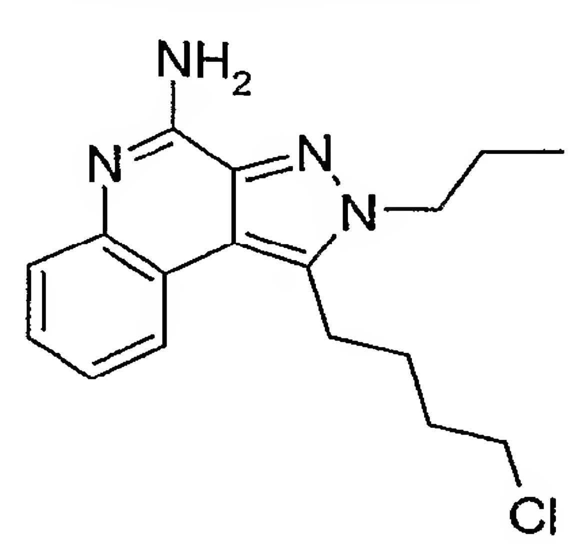
^{13}C-NMR (75 MHz, DMSO-d$_6$) δ 150.5, 143.7, 138.8, 135.4, 125.5, 121.6, 119.6, 116.0, 49.0, 32.3, 19.3, 18.3, 13.5, 13.1;

MS (APCI) *m/z* 269.3 (M+H)$^+$;

Anal. calcd for $C_{16}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.5; H, 7.54; N, 20.94.

Example 46

1-(4-Chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Ethyl 5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carboxylate was prepared using a modification of the procedure described in Part A of Example 19. Propylhydrazine oxalate

was used instead of ethylhydrazine oxalate. After all the reagents were added, the reaction mixture was stirred overnight instead of two hours. Crude ethyl 5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carboxylate was isolated as an impure brown oil, MS (APCI) *m/z* 273.1 $(M+H)^+$.

Part B

To a solution of the material from Part A (85.05 g, 0.312 mol) in ethanol (500 mL) was added 6 M aqueous sodium hydroxide (104 mL, 0.624 mol). The solution was stirred at ambient temperature for 2 hours. The ethanol was removed under reduced pressure and water (200 mL) was added. The aqueous solution was transferred to a separatory funnel and washed with diethyl ether (100 mL). The aqueous layer was acidified with 6 M aqueous hydrochloric acid to pH 3, causing a precipitate to form. After 10 minutes, the precipitate was isolated by filtration, washed with water, and dried under vacuum at 60 °C overnight to yield 57.1 g of a brown oil which was used without purification in the next step.

Part C

To a solution of the material from Part B (57.1 g, 0.233 mmol) in dichloromethane (600 mL) at 0 °C was added slowly a solution of oxalyl chloride (61.0 mL, 0.700 mmol) in dichloromethane (20 mL). The reaction was stirred for 10 minutes at 0 °C, then at ambient temperature for 4 hours. The solution was concentrated under reduced pressure, then was concentrated from dichloromethane twice. The residue was dissolved in dichloromethane (15 mL) and added dropwise to a flask containing concentrated ammonium hydroxide (250 mL) cooled in an ice bath. The reaction was stirred at ambient temperature overnight. The mixture was extracted with dichloromethane (600 mL, then 2 x 100 mL). The organic layers were combined, washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a brown solid that was purified by trituration with diethyl ether/hexanes. A tan solid was isolated by filtration to provide 30.98 g of 5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carboxamide. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.70 (br s, 1H), 6.59 (s, 1H), 5.32 (br s, 1H), 3.99 (t, J = 7.3 Hz, 2H), 3.61-3.54 (m, 2H), 2.69-2.59 (m, 2H), 1.94-1.76 (m, 6H), 0.94 (t, J = 7.4 Hz, 3H).

Part D

5-(4-Chlorobutyl)-1-propyl-1*H*-pyrazole-3-carboxamide (30.95 g, 0.127 mmol) in toluene (250 mL) was treated with phosphorous oxychloride (24.86 mL, 0.267 mol). The solution was heated at reflux for 40 minutes. The reaction was worked-up as described in Part D of Examples 37-39, with the exception that chloroform was used in place of methyl *tert*-butyl ether, to yield 5.20 g of 5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carbonitrile as an oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 1H), 4.04(t, J = 7.3 Hz, 2H), 3.62-3.53 (m, 2H), 2.70-2.58 (m, 2H), 1.94-1.76 (m, 6H), 0.93 (t, J = 7.4 Hz, 3H).

Part E

5-(4-Chlorobutyl)-1-propyl-1*H*-pyrazole-3-carbonitrile (14.00 g, 62.0 mmol) was converted into 4-bromo-5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carbonitrile acco rding the procedure described in Part F of Examples 1-4. Chloroform was used instead of dichloromethane in the extraction step during the work-up. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 10-25% ethyl acetate in hexanes) to provide 14.80 g of 4-bromo-5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carbonitrile as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.07 (t, J = 7.3 Hz, 2H), 3.59 (t, J = 6.1 Hz, 2H), 2.79-2.69 (m, 2H), 1.96-1.69 (m, 6H), 0.95 (t, J = 7.4 Hz, 3H).

Part F

To a mixture of 4-bromo-5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carbonitrile (8.25 g, 27.1 mmol) and powdered molecular sieves (1 g) in toluene (170 mL) was added 2-aminophenylboronic acid hydrochloride (9.40 g, 54.2 mmol), potassium phosphate (28.62 g, 135 mmol), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (0.701 g, 0.677 mmol) and bis(2-diphenylphosphinophenyl)ether (0.437 g, 0.812 mmol). Nitrogen gas was bubbled through the mixture for 5 minutes. The mixture was heated at 110 °C for 22 hours. After cooling to ambient temperature, the mixture was filtered through a plug of CELITE filter agent with 3:2 chloroform/methanol. The filtrate was concentrated under reduced pressure to yield a residue that was used in the next step.

Part G

Acetyl chloride (6.38 g, 81.3 mmol) was added to ethanol (20 mL) at 0 °C. The resulting solution was added to the residue from Part F. The solution was heated at reflux

overnight. Upon cooling to ambient temperature, the solution was concentrated under reduced pressure. The residue was partitioned between chloroform and 2 M aqueous sodium carbonate. The aqueous layer was extracted twice with chloroform, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-30% CMA in chloroform) followed by recrystallization from acetonitrile to afford 4.31 g of 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as off-white crystals, mp 172-173 °C.

^{1}H-NMR (300 MHz, DMSO-d$_6$) δ 7.93 (dd, J = 7.8, 1.1 Hz, 1H), 7.49 (dd, J = 8.1, 1.2 Hz, 1H), 7.36-7.27 (m, 1H), 7.24-7.15 (m, 1H), 6.62 (br s, 2H), 4.35 (t, J = 7.2 Hz, 2H), 3.73 (t, J = 6.4 Hz, 2H), 3.31-3.23 (m, 2H), 2.01-1.86 (m, 4H), 1.84-1.72 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H);

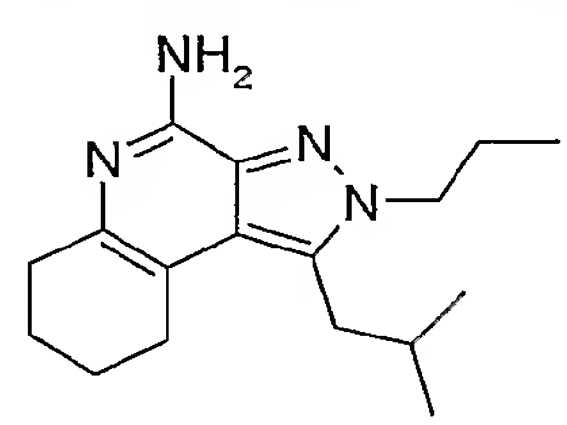
^{13}C-NMR (75 MHz, DMSO-d$_6$) δ 150.5, 143.7, 137.3, 135.5, 125.60, 125.55, 121.7, 121.5, 119.5, 116.3, 50.7, 44.9, 31.3, 25.7, 23.9, 23.5, 10.9;

MS (APCI) m/z 317.1 (M+H)$^+$;

Anal. calcd for $C_{17}H_{21}ClN_4$: C, 64.45; H, 6.68; N, 17.68. Found: C, 64.44; H, 6.88; N, 17.79.

Example 47

1-(2-Methylpropyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



A solution of 1-(2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (0.8 g, 3 mmol), prepared as described in Example 1, in trifluoroacetic acid (10 mL) was treated with platinum (IV) oxide (0.5 g) and shaken under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) for 24 hours on a Parr apparatus. The reaction mixture was diluted with chloroform (20 mL) and methanol (10 mL) and filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure. The residue was suspended in 6 M aqueous hydrochloric acid (5 mL), stirred for 30 minutes, and treated with 50%

aqueous sodium hydroxide to adjust the mixture to pH 13. A precipitate formed and was isolated by filtration, washed with water, and dried. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-35% CMA in chloroform) to yield 0.55 g of 1-(2-methylpropyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as an off-white powder, mp 167-168 °C.

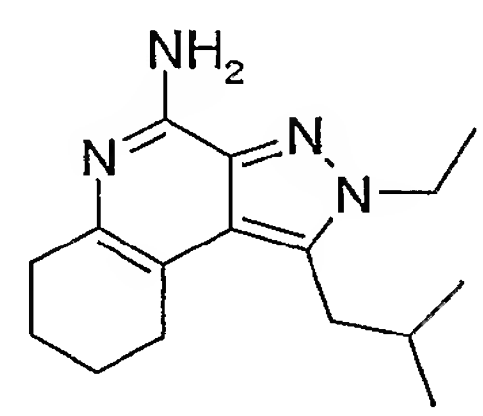
^{1}H-NMR (300 MHz, $CDCl_3$) δ 5.02 (br s, 2H), 4.26-4.16 (m, 2H), 2.94-2.83 (m, 4H), 2.79-2.69 (m, 2H), 2.05-1.92 (m, 3H), 1.89-1.76 (m, 4H), 0.97 (d, J = 6.7 Hz, 6H) 0.95 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.3, 141.2, 135.3, 134.9, 123.1, 112.1, 51.9, 34.2, 32.0, 30.7, 25.5, 23.9, 23.3, 23.0, 22.3, 11.2;

MS (APCI) *m/z* 287.2 $(M+H)^+$;

Anal. calcd for $C_{17}H_{26}N_4 \cdot 0.01\ CF_3COOH$: C, 71.09; H, 9.12; N, 19.48; F, 0.20. Found: C, 70.77; H, 9.37; N, 19.27; F, 0.22.

Example 48

2-Ethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



2-Ethyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (0.700 g, 1.61 mmol), prepared as described in Example 2, was reduced using the procedure described in Example 47. After chromatographic purification, the product was crystallized from acetonitrile to yield 0.39 g of 2-ethyl-1-(2-methylpropyl)-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white crystalline solid, mp 206-207 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 14.58 (br s, 1H), 10.88 (br s, 1H), 6.21 (br s, 1H), 4.33 (q, J = 7.3 Hz, 2H), 2.88 (d, J = 7.6 Hz, 2H), 2.86-2.71 (m, 4H), 1.95 (heptet, J = 6.9 Hz, 1H), 1.88-1.76 (m, 4H), 1.56 (t, J = 7.3 Hz, 3H), 0.99 (d, J = 6.7 Hz, 6H);

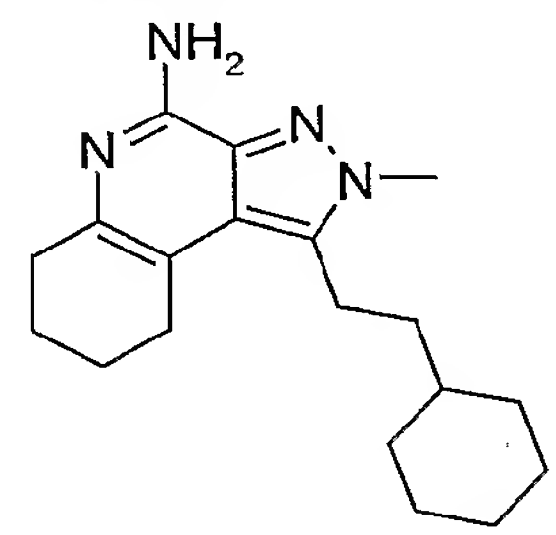
^{13}C-NMR (75 MHz, CDC13) δ 149.2, 137.0, 133.2, 131.6, 122.7, 112.2, 45.9, 33.9, 30.5, 26.5, 24.4, 22.3, 22.0, 21.6, 15.4;

MS (APCI) *m/z* 273.2 $(M+H)^+$;

Anal. calcd for $C_{16}H_{24}N_4 \cdot 1.02\ CF_3COOH$: C, 55.74; H, 6.49; N, 14.41; F, 14.96. Found: C, 55.41; H, 6.90; N, 14.38; F, 14.68.

Example 49

1-(2-Cyclohexylethyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



2-Methyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (0.79 g, 2.6 mmol), prepared as described in Example 40, was reduced using the procedure described in Example 47. After chromatographic purification, the product was crystallized from acetonitrile to yield 0.44 g of 1-(2-cyclohexylethyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white powder, mp 230-231 °C.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.96 (br s, 2H), 4.02 (s, 3H), 3.03-2.93 (m, 2H), 2.91-2.81 (m, 2H), 2.78-2.68 (m, 2H), 1.91-1.61 (m, 9H), 1.54-1.10 (m, 6H), 1.08-0.89 (m, 2H);

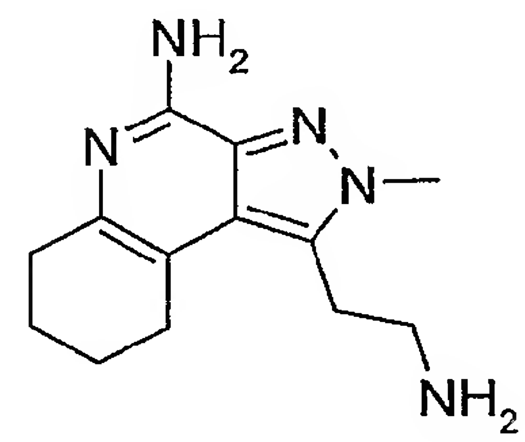
^{13}C-NMR (75 MHz, $CDCl_3$) δ 148.0, 141.3, 136.4, 135.2, 122.8, 112.0, 38.2, 37.8, 37.3, 33.1, 31.9, 26.5, 26.2, 25.1, 23.3, 22.9;

MS (APCI) *m/z* 313.2 $(M+H)^+$;

Anal. calcd for $C_{19}H_{28}N_4 \cdot 0.12\ H_2O$: C, 72.53; H, 9.05; N, 17.81. Found: C, 72.27; H, 9.16; N, 17.41.

Example 50

1-(2-Aminoethyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A modification of the method described in Part A of Example 11 was followed. A mixture of ethyl 2,4-dioxo-6-phthalimidohexanoate, sodium salt (prepared as described in Part A of Example 23, 100 g, 295 mmol) in glacial acetic acid (0.3 L) was cooled to 9 °C before the addition of methylhydrazine (16.0 mL, 300 mmol). During the addition, the reaction temperature did not exceed 16 °C. Solids were rinsed from the inside of the flask walls into the mixture with acetic acid (50 mL) and the mixture was allowed to warm to ambient temperature and stir overnight. Water was added to the mixture and additional solid precipitated. The solid was isolated by filtration, dried, and recrystallized from ethanol. The solid was isolated and dried to yield 75.2 g of ethyl 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carboxylate.

Part B

A solution of ethyl 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carboxylate (75.2 g, 230 mmol) in 1 M aqueous hydrochloric acid (450 mL) and acetic acid (450 mL) was heated at 100 °C (internal temperature) for 5.2 hours, cooled to ambient temperature, and stirred for about 12 hours. A white solid was isolated by filtration, washed with water, and dried to provide 52.6 g of 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carboxylic acid.

Part C

Toluene (250 mL) and thionyl chloride (30.4 mL, 418 mmol) were added to 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carboxylic acid (50.0 g, 167 mmol). The mixture was heated at reflux for 2 hours, cooled to ambient temperature, and poured onto ice. A solid was isolated by filtration, washed with water, and dried to afford 47.5 g of a white solid.

Part D

To a solid from Part C (25.0 g) in dichloromethane (250 mL) at 0 °C was added concentrated ammonium hydroxide (50 mL) in one portion. The mixture was stirred for 5 minutes, then hexanes (200 mL) was added and the mixture was filtered, washed with water, then dried to provide 13.07 g of 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carboxamide as a white powder.

Part E

To a mixture of 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carboxamide (10.5 g, 35.2 mmol) and pyridine (5.69 mL, 70.4 mmol) in dichloromethane (200 mL) at 0 °C was added trifluoroacetic anhydride (5.47 mL, 38.7 mmol) over two minutes. The solution was stirred at 0 °C for about 20 minutes, then was allowed to warm to ambient temperature. After 2 hours, more pyridine (2.8 mL) and trifluoroacetic anhydride (1.5 mL) were added. The reaction was quenched by adding 2 M sodium carbonate (200 mL). The mixture was extracted with chloroform. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to a volume of about 50 mL. A white solid was present. Heptane (150 mL) was added, and the mixture was concentrated to a volume of about 25 mL, then hexanes were added and the solid was collected by filtration. The white solid was washed with hexanes and dried to provide 8.50 g of 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carbonitrile that contained a small amount of an impurity.

Part F

To a mixture of 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carbonitrile (8.50 g, 30.3 mmol) and potassium acetate (4.50 g, 45.5 mmol) in acetic acid (40 mL) and dichloromethane (120 mL) was slowly added bromine (6.79 g, 42.5 mmol). The mixture was stirred overnight. Saturated aqueous sodium hydrogensulfite was added until the mixture became colorless, then the mixture was concentrated under reduced pressure to form a slurry. Water (200 mL) was added to the slurry and a white solid was isolated by filtration, washed with water, and dried to afford 9.15 g of 4-bromo-5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carbonitrile as a white solid.

Part G

A mixture of hydrazine hydrate (6.40 g, 127 mmol) and 4-bromo-5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-methyl-1*H*-pyrazole-3-carbonitrile (9.15 g, 25.5 mmol) in ethanol (200 mL) was heated at reflux for 80 minutes, then was allowed to cool to ambient temperature in a water bath. A precipitate formed and was isolated by filtration and washed with cold ethanol. The filtrate was concentrated under reduced pressure, and the resulting white solid was twice treated with toluene and concentrated under reduced pressure then dried under vacuum to provide 5.74 g of 5-(2-aminoethyl)-4-bromo-1-methyl-1*H*-pyrazole-3-carbonitrile as an off-white solid.

Part H

Di-*tert*-butyl dicarbonate (13.3 g, 60.9 mmol) was added to a mixture of 5-(2-aminoethyl)-4-bromo-1-methyl-1*H*-pyrazole-3-carbonitrile (11.62 g, 50.7 mmol) in 1-methyl-2-pyrrolidinone at 0 °C. The mixture was allowed to warm to ambient temperature and was stirred for 20 minutes; a solution formed. Water was added to the stirred solution, causing a solid to form. The mixture was cooled and the solid was isolated by filtration, washed with water, and dried. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 60-75% ethyl acetate in hexanes). The appropriate fractions were combined and concentrated under reduced pressure to provide 12.0 g of *tert*-butyl 2-(4-bromo-3-cyano-1-methyl-1*H*-pyrazol-5-yl)ethylcarbamate as a white solid.

Part I

A mixture of *tert*-butyl 2-(4-bromo-3-cyano-1-methyl-1*H*-pyrazol-5-yl)ethylcarbamate (19.1 g, 58.0 mmol), 2-aminophenylboronic acid hydrochloride (15.09 g, 87.03 mmol), triphenylphosphine (1.37 g, 5.22 mmol), palladium (II) acetate (390 mg, 1.74 mmol), 2 M aqueous sodium carbonate (87 mL, 174 mmol), 1-propanol (100 mL), and water (20 mL) was heated at 100 °C for 4 hours under a nitrogen atmosphere. Additional 1-propanol (100 mL) and water (20 mL) were added and the mixture was heated at 100 °C overnight. The mixture was allowed to cool to ambient temperature and chloroform (200 mL) was added. After 10 minutes, the mixture was transferred to a separatory funnel and the organic layer was isolated and washed with water (200 mL) and brine (200 mL). The combined organic layers were dried over sodium sulfate, filtered, and

concentrated to provide an oil that was purified by flash chromatography (silica gel, eluting sequentially with chloroform, 10% CMA in chloroform, and finally 40% CMA in chloroform) to yield an oil that was used in the next step.

Part J

Acetyl chloride (7.8 g, 100 mmol) was added to ethanol (100 mL) at 0 °C. The resulting solution was added to the oil from Part I. The solution was heated at reflux overnight. Upon cooling to ambient temperature, a precipitate formed that was isolated by filtration, washed with a small amount of cold ethanol, and dried under vacuum at 75 °C for 4 hours to give 7.34 g of 1-(2-aminoethyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride as a white solid.

Part K

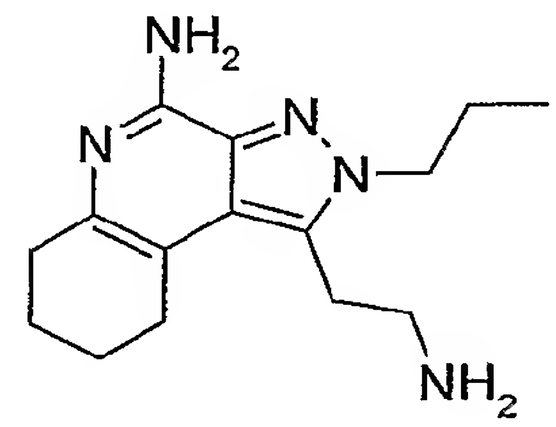
A solution of 1-(2-aminoethyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride (7.20 g, 22.9 mmol) in trifluoroacetic acid (75 mL) was treated with platinum (IV) oxide (7.0 g) and shaken under hydrogen pressure (50 psi, 3.4×10^5 Pa) for 24 hours on a Parr apparatus. The reaction mixture was diluted with chloroform (50 mL) and methanol (25 mL) and filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure. The residue was suspended in concentrated hydrochloric acid (5 mL), stirred for 2 hours, treated with 50% aqueous sodium hydroxide to adjust the pH to 13, and stirred at ambient temperature overnight. The mixture was diluted with water (100 mL) and was extracted with chloroform (5 x 150 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 5.10 g of 1-(2-aminoethyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as an off-white foam.

^{1}H-NMR (300 MHz, DMSO-d_6) δ 6.12-3.20 (br abs., 4H), 4.04 (s, 3H), 3.21-3.10 (m, 2H), 2.91-2.76 (m, 4H), 2.61-2.52 (m, 2H), 1.80-1.67 (m, 4H);

MS (APCI) *m/z* 246.3 $(M+H)^+$.

Example 51

1-(2-Aminoethyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A modification of the method described in Part A of Example 11 was followed. A mixture of ethyl 2,4-dioxo-6-phthalimidohexanoate, sodium salt (prepared as described in Part A of example 23, 67.9 g, 200 mmol) in glacial acetic acid (0.2 L) was cooled to 9 °C before the addition of propylhydrazine oxalate (32.8 g, 200 mmol). During the addition, the reaction temperature did not exceed 17 °C. The mixture was allowed to warm to ambient temperature and stir for 4 horus. Water (600 mL) was added to the mixture and additional solid precipitated. The solid was isolated by filtration, washed with water, and dried to yield 67.4 g of a yellow solid. The solid was stirred in 1 M aqueous potassium acetate (311 mL), isolated by filtration, washed with water, dried, and recrystallized from ethanol/heptane. The final solid was isolated, washed with 2:1 heptane/ethyl acetate, and dried to yield 45.2 g of ethyl 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carboxylate.

Part B

A stirred solution of ethyl 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carboxylate (45.1 g, 127 mmol) in 1 M aqueous hydrochloric acid (157 mL) and acetic acid (157 mL) was heated at 95 °C (internal temperature) for 10 hours and then cooled to 10 °C. Water (300 mL) was added and a white solid was isolated by filtration, washed with water and diethyl ether, and dried. The solid was treated with toluene (150 mL) and heated at reflux for 3 hours with a Dean-Stark trap. The mixture was cooled in an ice bath to 10 °C and a solid was isolated by filtration and dried to provide 28.85 g of 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carboxylic acid.

Part C

Toluene (70 mL) and thionyl chloride (70 mL) were added to 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carboxylic acid (28.8 g, 87.8 mmol) and the mixture was heated at reflux for 1 hour, cooled to ambient temperature, and concentrated under reduced pressure to yield a yellow solid. The solid was dissolved in dichloromethane (200 mL). The solution was cooled to 0 °C, then concentrated ammonium hydroxide (125 mL) was added in one portion. The resulting mixture was stirred for 1 hour at 0 °C. The dichloromethane was removed under reduced pressure. A solid was isolated by filtration, washed with water, and dried to afford 28.70 g of 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carboxamide.

Part D

To a mixture of 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carboxamide (16.3 g, 50.0 mmol) and pyridine (20.9 mL, 150 mmol) in dichloromethane (100 mL) at 0 °C was added a solution of trifluoroacetic anhydride (9.89 mL, 70.0 mmol) in dichloromethane (100 mL) over ten minutes. The solution was stirred at 0 °C for about 15 minutes, then was allowed to warm to ambient temperature. After 45 minutes, saturated aqueous sodium bicarbonate (200 mL) was added and the dichloromethane was removed under reduced pressure. A white solid was isolated by filtration, washed with water, and dried. The solid was recrystallized from 1:1 heptane/ethyl acetate to yield 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carbonitrile.

Part E

To a solution of 5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carbonitrile (14.1 g, 45.7 mmol) and potassium acetate (6.73 g, 68.6 mmol) in acetic acid (91 mL) and dichloromethane (46 mL) was slowly added bromine (3.28 g, 64.0 mmol). The mixture was stirred for one day. Saturated aqueous sodium hydrogensulfite was added until the mixture became colorless, then the mixture was concentrated under reduced pressure to form a slurry. Water (450 mL) was added to the slurry and a white solid was isolated by filtration, washed with water, and dried to afford 17.24 g of 4-bromo-5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carbonitrile as a white solid.

Part F

A mixture of hydrazine hydrate (11.1 g, 222 mmol) and 4-bromo-5-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]-1-propyl-1*H*-pyrazole-3-carbonitrile (17.2 g, 44.4 mmol) in ethanol (570 mL) was heated at reflux for 90 minutes, then was allowed to cool to ambient temperature. A precipitate was isolated by filtration and washed with cold ethanol. The filtrate was concentrated under reduced pressure to generate an off-white solid that was suspended in dichloromethane (133 mL). Di-*tert*-butyl dicarbonate (11.6 g, 53.3 mmol) was added to the mixture, which was then stirred overnight. The mixture was filtered and the filtrate was concentrated under reduced pressure to yield a yellow oil. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 40-60% ethyl acetate in hexanes). The appropriate fractions were combined and concentrated under reduced pressure to provide 15.8 g of *tert*-butyl 2-(4-bromo-3-cyano-1-propyl-1*H*-pyrazol-5-yl)ethylcarbamate as a colorless oil.

Part G

A flask containing a mixture of *tert*-butyl 2-(4-bromo-3-cyano-1-propyl-1*H*-pyrazol-5-yl)ethylcarbamate (15.8 g, 44.2 mmol), 2-aminophenylboronic acid hydrochloride (11.5 g, 66.3 mmol), triphenylphosphine (1.04 g, 3.98 mmol), palladium (II) acetate (299 mg, 1.33 mmol), 2 M aqueous sodium carbonate (67 mL, 133 mmol), 1-propanol (77.4 mL), and water (15.5 mL) was heated overnight under a nitrogen atmosphere in a 100 °C oil bath. The reaction was allowed to cool to ambient temperature and water (300 mL) was added. The mixture was extracted with chloroform, dried over magnesium sulfate, filtered, and concentrated to provide an oil that was purified twice by flash chromatography (silica gel, first column: eluted sequentially with 0-10% CMA in chloroform, and then 25% CMA in chloroform; second column: gradient elution with 50-60% ethyl acetate in hexanes) to yield 7.3 g of *tert*-butyl 2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)ethylcarbamate as a yellow resin.

Part H

Acetyl chloride (7.1 mL, 100 mmol) was added to ethanol (100 mL) at 0 °C. The resulting solution was added to the *tert*-butyl 2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)ethylcarbamate from Part G. The solution was heated at reflux for 9.5 hours. Upon cooling to ambient temperature, a precipitate formed that was isolated after

two days by filtration, washed with a small amount of cold ethanol, and dried to yield 5.78 g of 1-(2-aminoethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride as a white solid.

Part I

1-(2-Aminoethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride (2.50 g, 7.30 mmol) was reduced using the procedure described in Example 47. After the reaction was filtered and concentrated, the residue was triturated with diethyl ether to precipitate a solid that was isolated by filtration, washed with diethyl ether, and dried under vacuum. After chromatographic purification, the product was crystallized from acetonitrile to yield 0.44 g of the *bis*-trifluoroacetic acid salt of 1-(2-aminoethyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white powder, 228-230 °C. ^{1}H-NMR (300 MHz, DMSO-d_6) δ 13.13 (s, 1H), 9.30-6.50 (br peaks, 5H), 4.42 (t, J = 7.2 Hz, 2H), 3.47-3.33 (m, 2H), 3.11-2.92 (m, 2H), 2.87-2.75 (m, 2H), 2.68-2.57 (m, 2H), 1.99-1.86 (m, 2H) 1.86-1.68 (m, 4H);

MS (APCI) *m/z* 274.3 $(M+H)^+$.

Examples 52-55

A mixture of *tert*-butyl *N*-(2-pyridyl)carbamate (prepared as described in Part A of Example 15, 1.9 equivalents) in 1-propanol (15 mL) and 1 M aqueous HCl (15 mL) was heated at 80 °C for 1 hour. The reaction was allowed to cool to ambient temperature and solid sodium carbonate (1.5 equivalents) was added with stirring. A solution of a 4-bromo-1,5-disubstitued-1*H*-pyrazole-3-carbonitrile (1.51-2.07 g, 6.63-7.80 mmol, 1 equivalent) shown in the table below in 1-propanol (4-5 mL) was added, followed by triphenylphosphine (0.06 equivalent) and palladium (II) acetate (0.02 equivalent). In Example 55, tetrakis(triphenylphosphine)palladium(0) (0.05 equivalent) was used instead of triphenylphosphine and palladium (II) acetate. The flask was fitted with a reflux condenser and a nitrogen inlet line, then was placed under vacuum and back-filled with nitrogen three times. The pale yellow solution was heated under a nitrogen atmosphere at 100 °C for 18-21 hours. The 1-propanol was evaporated under reduced pressure. The remaining liquid was dissolved in chloroform (100 mL), washed with water (100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The

crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution using 0-30% CMA in chloroform). In Example 55, a gradient elution with 0-25% CMA in chloroform was used. The appropriate fractions were combined and concentrated to yield a pale yellow solid that was recrystallized from boiling acetonitrile. White crystals were isolated, washed with cold acetonitrile, and dried overnight at 60 °C in a vacuum oven to provide the product.

Example 52: Isolated 0.18 g of 1,2-diethyl-2*H*-pyrazolo[3,4-*c*]-1,8-naphthyridin-4-amine as off-white needles, mp 286-288 °C.

^{1}H NMR (300 MHz, d_6-DMSO) δ 8.46 (dd, J = 4.7, 1.9, 1H), 8.24 (dd, J = 7.8, 1.9, 1H), 7.16 (dd, J = 7.8, 4.7, 1H), 7.05 (s, 2H), 4.42 (q, J = 7.1, 2H), 3.24 (q, J = 7.5, 2H), 1.47 (t, J = 7.1 , 3H), 1.24 (t, J = 7.5, 3H);

^{13}C NMR (75 MHz, d_6-DMSO) δ 154.6, 153.0, 146.9, 139.8, 135.2, 129.8, 117.0, 115.8, 114.2, 44.5, 18.2, 15.9, 13.1;

Anal. calcd for $C_{13}H_{15}N_5$: C, 64.71; H, 6.27; N, 29.02. Found: C, 64.49; H, 6.31; N, 29.19.

Example 53: Isolated 90 mg of 1-ethyl-2-propyl-2*H*-pyrazolo[3,4-*c*]-1,8-naphthyridin-4-amine as off-white needles, mp 303-305 °C.

^{1}H NMR (300 MHz, d_6-DMSO) δ 8.46 (dd, J = 4.7, 1.9, 1H), 8.24 (dd, J = 7.8, 1.9, 1H), 7.16 (dd, J = 7.8, 4.7, 1H), 7.06 (s, 2H), 4.34 (q, J = 6.9, 2H), 3.24 (q, J = 7.5, 2H), 1.90 (sextet, J = 7.1, 2H), 1.26 (t, J = 7.8, 3H), 0.91 (t, J = 7.5, 3H);

^{13}C NMR (75 MHz, d_6-DMSO) δ 153.0, 149.5, 146.9, 140.3, 135.2, 129.8, 117.0, 115.7, 114.2, 50.9, 23.6, 18.2, 13.1, 10.9;

Anal. calcd for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.80; H, 6.67; N, 27.50.

Example 54: Isolated 0.156 g of 2-methyl-1-(2,2-dimethylpropyl)-2*H*-pyrazolo[3,4-*c*]-1,8-naphthyridin-4-amine as off-white needles, mp 323-326 °C.

^{1}H NMR (300 MHz, d_6-DMSO) δ 8.49 (dd, J = 7.9, 1.9, 1H), 8.44 (dd, J = 4.6, 1.6, 1H), 7.12 (dd, J = 7.8, 4.7, 1H), 7.08 (s, 2H), 4.10 (s, 3H), 3.23 (s, 2H), 0.99 (s, 9H);

^{13}C NMR (75 MHz, d_6-DMSO) δ 154.8, 153.0, 147.0, 137.5, 135.0, 130.5, 117.5, 116.4, 114.4, 38.4, 37.0, 35.3, 29.4;

Anal. calcd for $C_{15}H_{19}N_5$: C, 66.89; H, 7.11; N, 26.00. Found: C, 66.95; H, 6.95; N, 26.08.

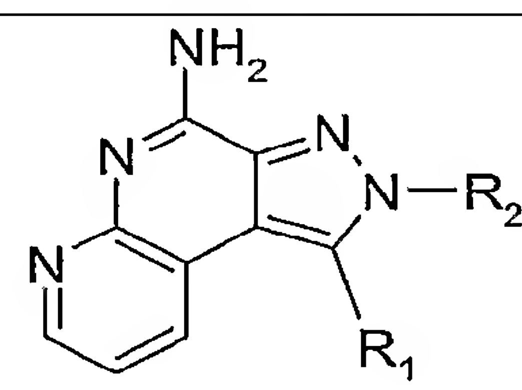
Example 55: Isolated 0.24 g of 2-benzyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]-1,8-naphthyridin-4-amine as off-white needles, mp 232-235 °C.

^{1}H NMR (300 MHz, d_6-DMSO) δ 8.46 (dd, *J* = 4.4, 1.6, 1H), 8.28 (dd, *J* = 7.8, 1.9, 1H), 7.36-7.27 (m, 3H), 7.19-7.13 (m, 5H), 5.70 (s, 2H), 3.12 (d, *J* = 8.5, 2H), 1.95 (septet, *J* = 6.9, 1H), 0.92 (d, *J* = 6.6, 6H);

^{13}C NMR (75 MHz, d_6-DMSO) δ 154.8, 153.1, 147.1, 138.9, 136.9, 135.6, 130.2, 128.6, 127.6, 126.7, 116.9, 114.1, 53.3, 33.2, 28.6, 21.8;

Anal. calcd for $C_{20}H_{21}N_5$: C, 72.48; H, 6.39; N, 21.13. Found: C, 72.24; H, 6.56; N, 21.18.

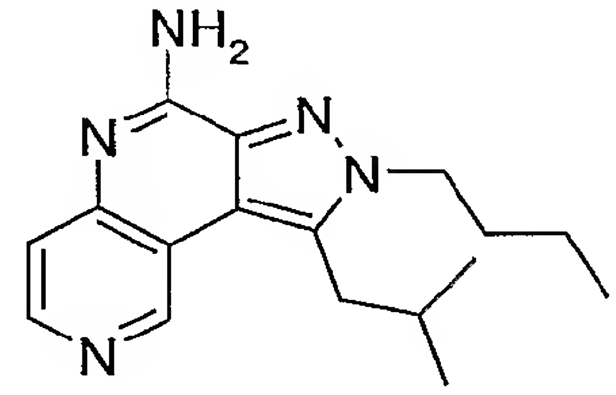
Examples 52-55



Example	Starting Material	R_1	R_2
52	4-Bromo-1,5-diethyl-1*H*-pyrazole-3-carbonitrile (prepared Example 11)	$-CH_2CH_3$	$-CH_2CH_3$
53	4-Bromo-5-ethyl-1-propyl-1*H*-pyrazole-3-carbonitrile (prepared in Example 44)	$-CH_2CH_3$	$-CH_2CH_2CH_3$
54	4-Bromo-1-methyl-5-(2,2-dimethylpropyl)-1*H*-pyrazole-3-carbonitrile (prepared in Example 37)	$-CH_2C(CH_3)_3$	$-CH_3$
55	4-Bromo-1-benzyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile (prepared in Example 8)	$-CH_2CH(CH_3)_2$	$-CH_2C_6H_5$

Example 56

2-Butyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]-1,6-naphthyridin-4-amine



Part A

A 2.5 M solution of *n*-butyl lithium in hexane (100 mL, 250 mmol) was added over 20 minutes to a stirred solution of *tert*-butyl pyridin-4-ylcarbamate (19.4 g, 100 mmol) and N,N,N′,N′-tetramethylethylenediamine (31.4 g, 270 mmol) in THF (500 mL) at –78 °C. *tert*-Butyl pyridin-4-ylcarbamate is available from a literature procedure (Spivey, A. C. *et al. J. Org. Chem.* 1999, *64*, 9430-9443). A white solid appeared and the mixture was stirred for 10 minutes at –78 °C, then was allowed to warm slowly to –4 °C before cooling to –78 °C again. Trimethyl borate (39.5 g, 380 mmol) was added over 15 minutes. The solution was allowed to warm to 0 °C, then was poured into saturated aqueous ammonium chloride (500 mL). The mixture was stirred for 2 minutes. After standing at ambient temperature overnight, the mixture was partitioned between diethyl ether and brine. The organic layer was separated and washed with brine. A white solid formed in the organic layer and was isolated by filtration. The solid was washed sequentially with diethyl ether, water, and diethyl ether, then was dried to provide 17.1 g of 4-[(*tert*-butoxycarbonyl)amino]pyridin-3-ylboronic acid as a white solid.

Part B

2-Butyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]-1,6-naphthyridin-4-amine was synthesized from 4-[(*tert*-butoxycarbonyl)amino]pyridin-3-ylboronic acid (2.48 g, 10.4 mmol) and 4-bromo-1-butyl-5-(2-methylpropyl)-1*H*-pyrazole-3-carbonitrile (prepared as described in Parts A-F of Example 4, 1.56 g, 5.49 mmol) according to the reaction conditions described in Examples 52-54. Additional palladium (II) acetate (50 mg) and triphenylphosphine (170 mg) were added after the reaction had been heated for 23 hours. After the addition, the flask was placed under vacuum and back-filled with nitrogen twice. The solution was heated at 100 °C for an additional 29 hours. The reaction was worked-up and purified as described in Example 54, but was not recrystallized from acetonitrile, to

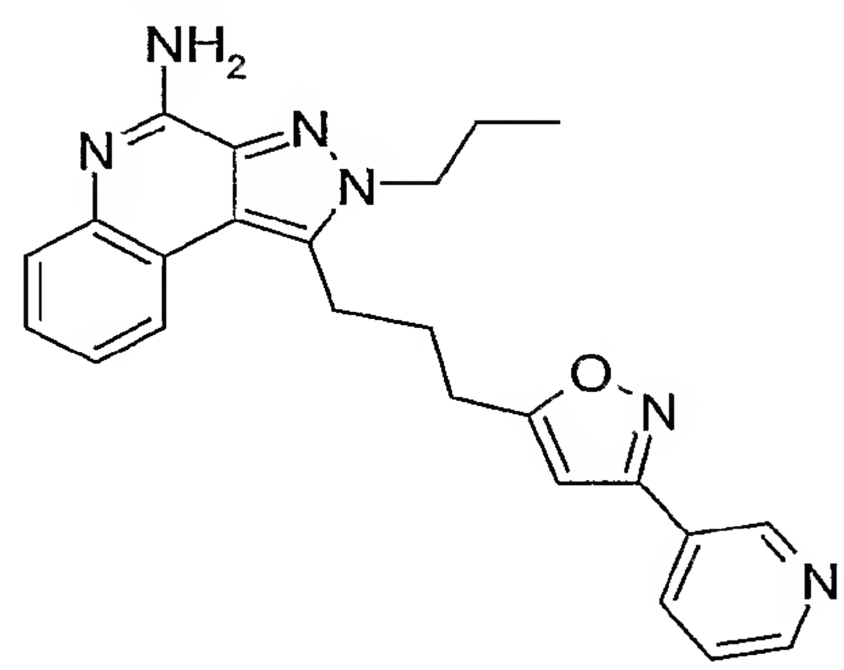
provide 25 mg of 2-butyl-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]-1,6-naphthyridin-4-amine as an off-white solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 9.10 (s, 1H), 8.31 (d, *J* = 5.4, 1H), 7.30 (d, *J* = 5.4, 1H), 7.25 (s, 2H), 4.37 (t, *J* = 7.2, 2H), 3.17 (d, *J* = 7.5, 2H), 2.10-1.86 (m, 3H), 1.39-1.32 (m, 2H), 0.99 (d, *J* = 6.6, 6H), 0.92 (t, *J* = 7.6, 3H);

HRMS Measured Mass $(M+H)^+$ 298.2023.

Example 57

2-Propyl-1-[3-(3-pyridin-3-ylisoxazol-5-yl)propyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A mixture of 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 46, 5.00 g, 15.8 mmol), 4-dimethylaminopyridine (0.04 g, 0.316 mmol), di-*tert*-butyldicarbonate (13.8 g, 63.12 mmol), and triethylamine (5.50 mL, 39.5 mmol) was heated at 90 °C for 20 minutes and a solution formed. The temperature was decreased to 60 °C and the solution was heated for 1 hour. The solution was allowed to cool to ambient temperature and was concentrated under reduced pressure. The resulting oil was partitioned between dichloromethane and 1 M aqueous potassium hydroxide. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated to a yield an oil that was dried under vacuum. The oil was triturated with an approximately 1:1 diethyl ether/hexanes solution, resulting in the formation of a solid that was isolated by filtration and dried to provide 5.68 g of di(*tert*-butyl) 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as a tan solid.

Part B

Potassium acetate (0.83 g, 8.432 mmol) and sodium iodide (16 g, 1.05 mmol) was added to a solution of di(*tert*-butyl) 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (2.18 g, 4.22 mmol) in DMF (15 mL). The reaction mixture was heated at 90 °C under a nitrogen atmosphere for 4.5 hours. The reaction was allowed to cool to ambient temperature and the volatiles were removed under reduced pressre. The resulting oil was partitioned between ethyl acetate and water. The organic layer was isolated and washed with water (2 x 25 mL) and brine (3 x 20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield an oil that was dried under vacuum to provide 1.76 g of 4-{4-[bis(*tert*-butoxycarbonyl)amino]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl}butyl acetate.

Part C

Potassium carbonate (6 mg, 0.041 mmol) was added to a solution of 4-{4-[bis(*tert*-butoxycarbonyl)amino]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl}butyl acetate (0.8823 g, 1.632 mmol) in methanol (5 mL). The mixture was stirred at ambient temperature for 1.3 hours. The volatiles were removed under reduced pressure. The resulting oil was purified by flash chromatography (silica gel, eluted with 100% ethyl acetate) to yield 0.1466 g of di(*tert*-butyl) 1-(4-hydroxybutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate in about 87% purity.

Part D

To dichloromethane (5 mL) at –78 °C was added dimethylsulfoxide (0.12 mL, 1.6 mmol) and oxalyl chloride (0.11 mL, 1.2 mmol). After several minutes, a solution di(*tert*-butyl) 1-(4-hydroxybutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (0.5449 g, 1.093 mmol) and triethylamine (0.46 mL, 3.3 mmol) in dichloromethane (5 mL) was added dropwise to the –78 °C solution. After 15 minutes, the cooling bath was removed and the solution was allwed to warm to ambient temperature, during which time more dichloromethane (20 mL) was added. The solution was transferred to a separatory funnel and washed with aqueous potassium carbonate, water, and brine. The solution was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The resulting oil was dried under vacuum to yield 0.5845 g of di(*tert*-butyl) 1-(4-oxobutyl)-2-propyl-2*H*-

pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate that contained a small amount of dimethylsulfoxide, but was used without further purification.

Part E

Diethyl 1-diazo-2-oxopropylphosphonate (0.28 g, 1.3 mmol) was prepared by the method of Bestmann, H. J. *et al.*, *Synlett,* 1996, *6*, 521-522 and added to a stirred mixture of di(*tert*-butyl) 1-(4-oxobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (0.543 g, 1.09 mmol) and potassium carbonate (0.31 g, 2.2 mmol) in methanol (5 mL) at ambient temperature. After 4 hours, the reaction was concentrated under reduced pressure. The oil was dissolved in dichloromethane, washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, eluted with 5% ethyl acetate in dichloromethane) to yield 0.2498 g of a white solid that was used without further purification in the next step.

Part F

N-Chlorosuccinimide (0.15 g, 1.0 mmol) was added to a solution of 3-pyridine aldoxime (0.13 g, 1.0 mmol) in THF (5 mL). The solution was stirred at ambient temperature for 1 day. The material from Part E (0.2498 g, 0.5071 mmol) and anhydrous triethylamine (0.16 mL, 1.1 mmol) were added and the solution was heated at 60 °C for 20 hours. The volatiles were removed under reduced pressure to yield a brown oil that was purified by flash chromatography (silica gel, sequential elution with 40% ethyl acetate in hexanes, 40% ethyl acetate in dichloromethane, and finally 100% ethyl acetate) to yield 0.1105 g of material that was used without further purification in the next step.

Part G

A solution of the material from Part F (0.1105 g) in a solution of 1:1 ethanol/concentrated hydrochloric acid was heated at 60 °C under a nitrogen atmosphere for 2 hours. The volatiles were removed under reduced pressure. The resulting oil was dissolved in water and 1 drop of 50% aqueous sodium hydroxide was added to adjust the pH to 14. The mixture was extracted with dichloromethane several times. The organic layers were combined, washed with water and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield an oil. The oil was dried under vacuum, then triturated with hexanes to yield a solid that was isolated by filtration. The solid was dried under vacuum at 70 °C to yield 0.0376 g of 2-propyl-1-[3-(3-pyridin-3-

ylisoxazol-5-yl)propyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white powder, mp 192.0-193.0 °C.

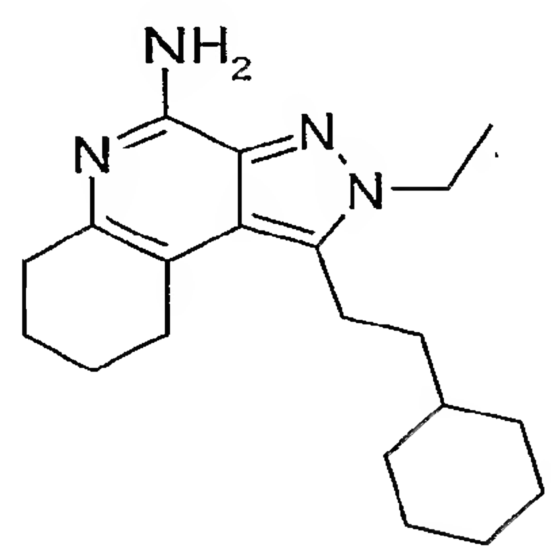
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.99 (dm, J = 1.5 Hz, 1H), 8.68 (dm, J = 3.2 Hz, 1H), 8.11 (dm, J = 8.0 Hz, 1H), 7.81(d, J= 6.7 Hz, 1H), 7.70 (d, J = 7.1 Hz, 1H), 7.40-7.43 (m, 2H), 7.23-7.28 (m, 1H), 6.38 (s, 1H), 5.36 (s, 2H), 4.29 (t, J = 7.4 Hz, 2H), 3.47 (t, J = 7.9 Hz, 2H), 3.03 (t, J = 7.3 Hz, 2H), 2.26 (t, J = 7.9 Hz, 2H), 1.98 (q, J = 7.3 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H);

MS (APCI) m/z 412 $(M + H)^+$;

Anal. calcd for $C_{24}H_{24}N_6O \cdot 0.2C_2H_6O$: C, 69.50; H, 6.02; N, 19.93. Found: C, 69.15; H, 5.75; N, 20.09.

Example 58

1-(2-Cyclohexylethyl)-2-ethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



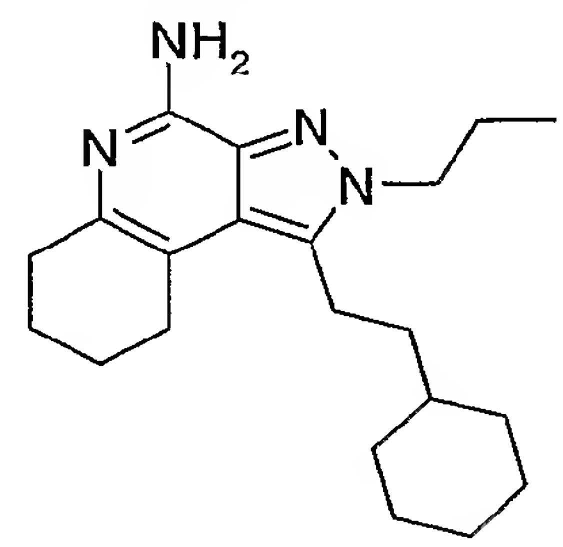
A mixture of 2-ethyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 41, 575 mg, 1.81 mmol) and platinum (IV) oxide (290 mg) in trifluoroacetic acid (8 mL) was shaken under hydrogen pressure (50 psi, 3.4×10^5 Pa) for 22.5 hours on a Parr apparatus. The reaction mixture was filtered through a poly(tetrafluoroethylene) membrane to remove the catalyst. The filtrate was concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution using 0-30% CMA in chloroform) and the appropriate fractions were concentrated to yield a solid that was slurried in hot acetonitrile. The mixture was allowed to cool to ambient temperature with stirring, then 318 mg of 1-(2-cyclohexylethyl)-2-ethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was isolated as a white powder, mp 177.0-179.0 °C.

MS (APCI) m/z 327 $(M + H)^+$;

Anal. calcd for $C_{20}H_{30}N_4$: C, 73.58; H, 9.26; N, 17.16. Found: C, 73.48; H, 9.01; N, 17.16.

Example 59

1-(2-Cyclohexylethyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



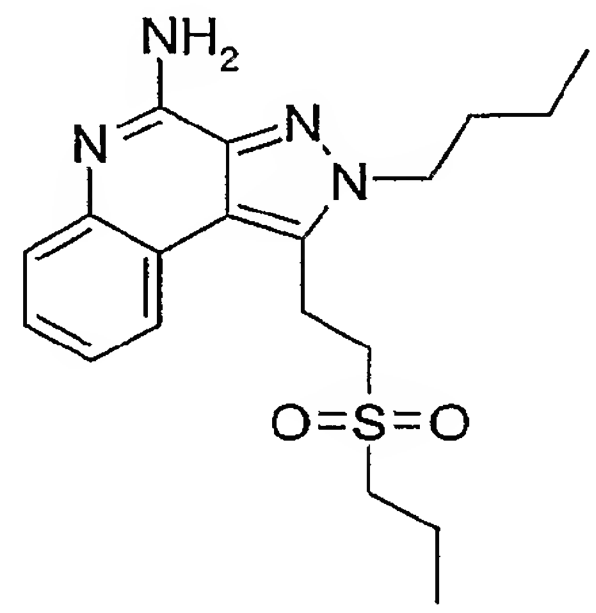
A mixture of 1-(2-phenylethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 42, 400 mg, 1.21 mmol) and platinum (IV) oxide (200 mg) in trifluoroacetic acid (8 mL) was shaken under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) on a Parr apparatus for 18 hours and worked up using the method described in Example 58 to afford 217 mg of 1-(2-cyclohexylethyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white powder, mp 173-174.5 °C.

MS (APCI) *m/z* 341 $(M + H)^+$;

Anal. calcd for $C_{21}H_{32}N_4$: C, 74.07; H, 9.47; N, 16.45. Found: C, 73.77; H, 9.73; N, 16.49.

Example 60

2-Butyl-1-[2-(propylsulfonyl)ethyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Solid sodium hydride (60% dispersion in oil, 2.90 g, 72.3 mmol) was added in portions over 5 minutes to a stirred solution of 1-propanethiol (6.00 g, 78.8 mmol) in tetrahydrofuran (262 mL). After 15 minutes, a thick white suspension had formed. To the suspension was added 1-chloro-3-butanone (7.00 g, 65.7 mmol), which caused the reaction mixture to warm and a cloudy solution to form. After 30 minutes, the cloudy solution was partitioned between ethyl acetate (100 mL) and water (100 mL). The layers were separated and the organic layer was washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to afford a pale brown oil. The crude product was purified by flash chromatography (silica gel, elution with 20% ethyl acetate in hexanes) to provide 9.0 g of 4-(propylthio)butan-2-one as a clear liquid.

Part B

A neat mixture of 4-(propylthio)butan-2-one (9.00 g, 61.5 mmol) and diethyl oxalate (9.00 g, 61.5 mmol) was added dropwise to a stirred solution of sodium *tert*-butoxide (5.90 g, 61.5 mmol) in ethanol (44 mL) at ambient temperature. Following the addition, the reaction was stirred for two hours. Acetic acid (35 mL) was added, followed by potassium acetate (7.24 g, 73.8 mmol). The mixture was cooled in a cold water bath. Butylhydrazine (11.0 g, 61.5 mmol) was added in portions. After 15 minutes, the mixture was allowed to warm to ambient temperature and was stirred for 2 hours. The volatiles were removed under reduced pressure to yield an oil. Saturated aqueous sodium carbonate was added to the oil until a pH of 10 was reached. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine, dried

over sodium sulfate, filtered, and concentrated under reduced pressure. The orange oil was purified by flash chromatography (silica gel, elution with 20% ethyl acetate in hexanes) to provide 10.6 g of ethyl 1-butyl-5-[2-(propylthio)ethyl]-1*H*-pyrazole-3-carboxylate as an orange oil.

Part C

To a stirred solution of 1-butyl–5-[2-(propylthio)ethyl]-1*H*-pyrazole-3-carboxylate (10.6 g, 35.5 mmol) in chloroform (355 mL) was added mCPBA (20.4 g, 71.0 mmol) in portions over 15 minutes. After 1 hour, the mixture was partitioned between chloroform and saturated aqueous sodium carbonate (100 mL). The layers were separated and the organic layer was washed with saturated aqueous sodium carbonate (100 mL) and brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford an oil. The crude product was purified by flash chromatography (silica gel, elution with 20% ethyl acetate in hexanes) to afford 5.65 g of ethyl 1-butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole-3-carboxylate.

Part D

To a solution of ethyl 1-butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole-3–carboxylate (5.00 g, 15.1 mmol) in ethanol (76 mL) at ambient temperature was added 6 M aqueous sodium hydroxide (5.0 mL, 30 mmol). The solution was stirred for 2 hours, then the volatiles were removed under reduced pressure and the resulting oil was dissolved in water (100 mL). The aqueous solution was washed with dichloromethane (50 mL) and then the pH was adjusted with 1 M hydrochloric acid to pH 4. A precipitate formed and the mixture was stirred for 1 hour. The solid was isolated by filtration, washed with water, and dried to provide 4.6 g of 1-butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole-3-carboxylic acid as a white powder.

Part E

To a solution of 1-butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole-3-carboxylic acid (4.00 g, 13.22 mmol) in dichloromethane (66 mL) was added oxalyl chloride (3.5 mL, 39.7 mmol) and a drop of DMF. The solution bubbled vigorously and was stirred at ambient temperature for 30 minutes. The solution was concentrated under reduced pressure. The residue was dissolved in dichloromethane (66 mL) and the resulting solution was cooled in an ice bath, then concentrated ammonium hydroxide (66 mL) was added dropwise. After

the addition was complete, the ice bath was removed and the mixture was stirred at ambient temperature for 2 hours. The volatiles were removed under reduced pressure to afford a slurry that was extracted with chloroform (2 x 100 mL). The organic layers were combined and concentrated under reduced pressure to afford 4.0 g of 1-butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole-3-carboxamide as a white solid.

Part F

1-Butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole-3-carboxamide (4.00 g, 13.27 mmol) in toluene (66 mL) was treated with phosphorous oxychloride (2.50 mL, 26.5 mol). The solution was heated at reflux for 1 hour. The reaction mixture was allowed to cool to ambient temperature and the volatiles were removed under reduced pressure. The resulting oil was diluted with water (50 mL) and saturated aqueous sodium bicarbonate. The mixture was extracted with dichloromethane (2 x 50 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate (50 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 3.8 g of 1-butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole-3-carbonitrile as a brown oil.

Part G

Bromine (0.8 mL, 14.7 mmol) was added dropwise to a stirred solution of potassium acetate (2.00 g, 20.1 mmol) and 1-butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole-3-carbonitrile (3.80 g, 13.4 mmol) in acetic acid (27 mL). The reaction was stirred at ambient temperature, then was concentrated under reduced pressure to afford a solid. Saturated aqueous sodium bicarbonate was added to the solid until the mixture was pH 9. The mixture was extracted with dichloromethane (2 x 50 mL). The organic layers were combined and concentrated under reduced pressure to afford a brown oil. The crude product was purified by flash chromatography (silica gel, elution with 40% ethyl acetate in hexanes) to yield 2.85 g of 4-bromo-1-butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole–3-carbonitrile as a white solid.

Part H

To a mixture of 4-bromo-1-butyl-5-[2-(propylsulfonyl)ethyl]-1*H*-pyrazole-3-carbonitrile (2.35 g, 6.49 mmol) and powdered molecular sieves (1 g) in toluene (41 mL) was added 2-aminophenylboronic acid hydrochloride (2.25 g, 12.97 mmol), potassium phosphate (6.90 g, 32.5 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.148 g, 0.162

mmol) and bis(2-diphenylphosphinophenyl)ether (0.105 g, 0.195 mmol). Nitrogen gas was bubbled through the mixture for 5 minutes. The mixture was heated at 110 °C for 20 hours. After cooling to ambient temperature, the mixture was filtered through a plug of CELITE filter agent, which was rinsed until clear with a solution of dichloromethane and methanol. The filtrate was concentrated under reduced pressure to yield a residue that was used in the next step.

Part I

The material from Part H was dissolved in ethanol (24 mL) and a solution of hydrogen chloride in ethanol (2.7 M, 7.0 mL, 19 mmol) was added. The solution was heated at reflux for 2.5 hours. Upon cooling to ambient temperature, the solution was concentrated under reduced pressure. The resulting oil was dissolved in water and the pH was adjusted with saturated aqueous sodium carbonate to pH 10. The solution was extracted with dichloromethane (3 x 50 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, elution with 5% methanol in dichloromethane) to yield an off-white foam (1.50 g) that was crystallized from ethanol (20 mL). The crystals were isolated by filtration, washed with ethanol, and dried under vacuum at 65 °C for 10 hours to yield 2-butyl-1-[2-(propylsulfonyl)ethyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as tan crystalline plates, mp 169-171 °C.

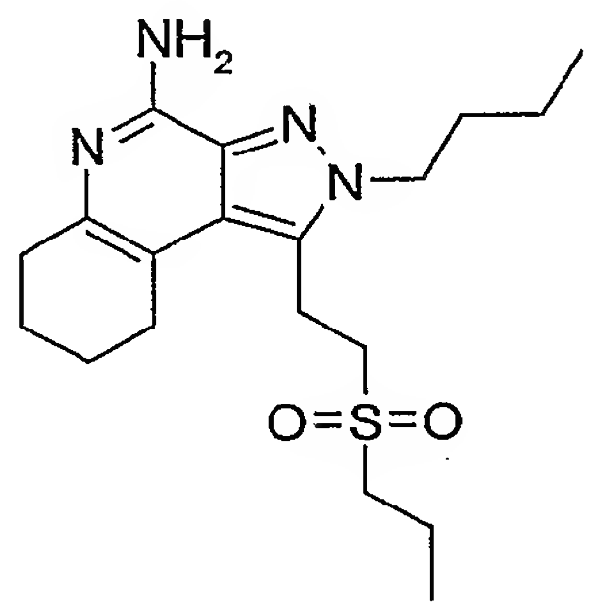
^{1}H NMR (300 MHz, DMSO-d_6) δ 7.90 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.35 (t, J = 8.1 Hz, 1H), 7.21 (t, J = 8.1 Hz, 1H), 6.69 (bs, 2H), 4.42 (t, J = 7.5 Hz, 2H), 3.70-3.66 (m, 2H), 3.51-3.46 (m, 2H), 3.23-3.18 (m, 2H) 1.90 (pentet, J = 7.5 Hz, 2H), 1.74 (sextet, J = 7.5 Hz, 2H), 1.37 (sextet, J = 7.5 Hz, 2H), 0.99 (t, J = 7.5 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H);

MS (ESI) m/z 375 $(M + H)^+$;

Anal. Cacld for $C_{19}H_{26}N_4O_2S$: C, 60.94; H, 7.00: N, 14.96. Found: C, 60.85; H, 6.92; N, 14.90.

Example 61

2-Butyl-1-[2-(propylsulfonyl)ethyl]-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



A solution of 2-butyl-1-[2-(propylsulfonyl)ethyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 60, 0.50 g, 1.3 mmol) in trifluoroacetic acid (6 mL) was treated with platinum (IV) oxide (0.5 g) and shaken under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) for 20 hours on a Parr apparatus. The reaction mixture was filtered through a layer of CELITE filter agent, and the CELITE filter agent was rinsed with dichloromethane (100 mL) until the rinses were clear. The filtrate was concentrated under reduced pressure. The oil was suspended in water (20 mL) and treated with 50% aqueous sodium hydroxide to adjust the mixture to pH 14, causing a precipitate to form. The mixture was stirred for 1 hour, then the precipitate was isolated by filtration and washed with water. The white powder was recrystallized from acetonitrile (5 mL). The crystals were isolated by filtration, washed with acetonitrile, and dried under vacuum at 65 °C to afford 0.40 g of 2-butyl-1-[2-(propylsulfonyl)ethyl]-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as white crystals, mp 173-175 °C.

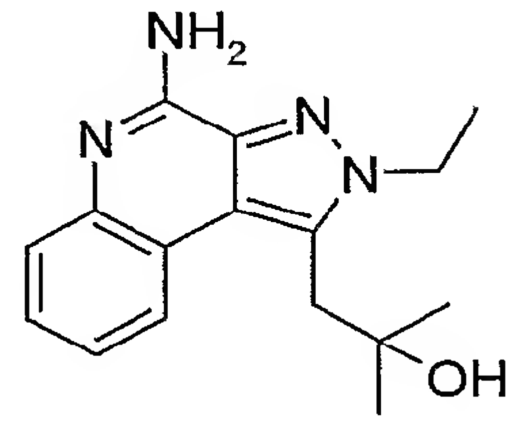
^{1}H NMR (300 MHz, DMSO-d_6) δ 6.02 (bs, 2H), 4.28 (t, J = 7.5 Hz, 2H), 3.43-3.37 (m, 4H), 3.19-3.14 (m, 2H), 2.85 (bs, 2H) 2.56 (bs, 2H), 1.85 (pentet, J = 7.5 Hz, 2H), 1.77-1.70 (m, 6H), 1.33 (sextet, J = 7.5 Hz, 2H), 1.00 (t, J = 7.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 3H);

MS (ESI) m/z 379 $(M + H)^+$;

Anal. Cacld for $C_{19}H_{30}N_4O_2S$: C, 60.29; H, 7.99: N, 14.80. Found: C, 59.98; H, 8.34; N, 15.11.

Example 62

1-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol



Part A

A solution of mesityl oxide (30.0 mL, 262 mmol) and diethyl oxalate (35.6 mL, 262 mmol) was added dropwise to a stirred solution of sodium *tert*-butoxide (54.1 g, 563 mmol) in ethanol (187 mL) at ambient temperature according to the procedure described in Part B of Example 60. The reaction was stirred for 1 hour, then was treated with acetic acid (131 mL), potassium acetate (38.6 g, 393 mmol), and ethylhydrazine oxalate (43.2 g, 288.2 mmol) according to the procedure described in Part B of Example 60. The mixture was stirred overnight at ambient temperature. The volatiles were removed under reduced pressure and the residue was diluted with water and chloroform. 2 M aqueous sodium carbonate was added until pH 11 was reached. The mixture was extracted with chloroform. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a black oil that was used without purification in the next step.

Part B

A mixture of the material from Part A, concencentrated ammonium hydroxide (500 mL) and methanol (200 mL) were stirred at ambient temperature for 16 hours. A white solid was isolated from the mixture by filtration. More solid was isolated from the filtrate to yield a total for 13.9 g of 1-ethyl-5-(2-methylprop-1-enyl)-1*H*-pyrazole-3-carboxamide.

Part C

A mixture of 1-ethyl-5-(2-methylprop-1-enyl)-1*H*-pyrazole-3-carboxamide (5.0 g, 25.9 mmol) and phosphorous oxychloride (18.5 mL) was heated at 90 °C for 20 minutes. The reaction vessel was cooled in an ice bath and reaction mixture was poured over ice (100 mL). The quenched reaction mixture was made basic with 2 M aqueous sodium carbonate and was extracted with chloroform. The organic layers were dried over sodium

sulfate, filtered, and concentrated under reduced pressure to provide 1-ethyl-5-(2-methylprop-1-enyl)-1*H*-pyrazole-3-carbonitrile, all of which was used in the next step.

Part D

A solution of the material from Part C and mCPBA (11.7 g, 34.0 mmol) in dichloromethane (115 mL) was stirred at ambient temperature overnight. The resulting mixture was diluted with water and the pH was made basic with 2 M aqueous sodium carbonate. The solution was extracted with chloroform. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 5-(3,3-dimethyloxiran-2-yl)-1-ethyl-1*H*-pyrazole-3-carbonitrile, all of which was used in the next step.

Part E

Bromine (1.7 mL, 33.0 mmol) was added to a solution of the material from Part D in chloroform at 0 °C. The red solution was stirred at ambient temperature for 2 hours, then saturated aqueous sodium bisulfite was added and the mixture was concentrated under reduced pressure. The residue was diluted with chloroform (100 mL) and the pH was adjusted with 2 M aqueous sodium carbonate to pH 11. The cloudy mixture was diluted with water (50 mL) and was extracted with chloroform (3 x 75 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 4.4 g of a cloudy oil that was used without purification in the next step.

Part F

To a mixture of the material from Part E in toluene (62 mL) at ambient temperature was added azobisisobutyronitrile (AIBN, 512 mg, 3.12 mmol) and tributyltin hydride (4.0 mL, 15.0 mmol). Bubbles were observed for a short period of time. The pale yellow solution was heated at 90 °C for 1 hour. The solution was allowed to cool to ambient temperature and subjected to chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-50% ethyl acetate in hexanes to afford 1.1 g of 4-bromo-1-ethyl-5-(2-hydroxy-2-methylpropyl)-1*H*-pyrazole-3-carbonitrile as a colorless oil.

Part G

To a mixture of 4-bromo-1-ethyl-5-(2-hydroxy-2-methylpropyl)-1*H*-pyrazole-3-carbonitrile (1.0 g, 3.7 mmol) and powdered molecular sieves (1 g) in toluene (23 mL) was

added 2-aminophenylboronic acid hydrochloride (1.28 g, 7.4 mmol), potassium phosphate (3.92 g, 18.5 mmol), tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (96 mg, 0.093 mmol) and bis(2-diphenylphosphinophenyl)ether (60 mg, 0.111 mmol). Nitrogen gas was bubbled through the mixture for 5 minutes. The mixture was heated at 110 °C for 1 day. After cooling to ambient temperature, the mixture was filtered through a plug of silica gel, which was rinsed with a solution of 3:2 chloroform/methanol. The filtrate was concentrated under reduced pressure to yield a residue that was used in the next step.

Part H

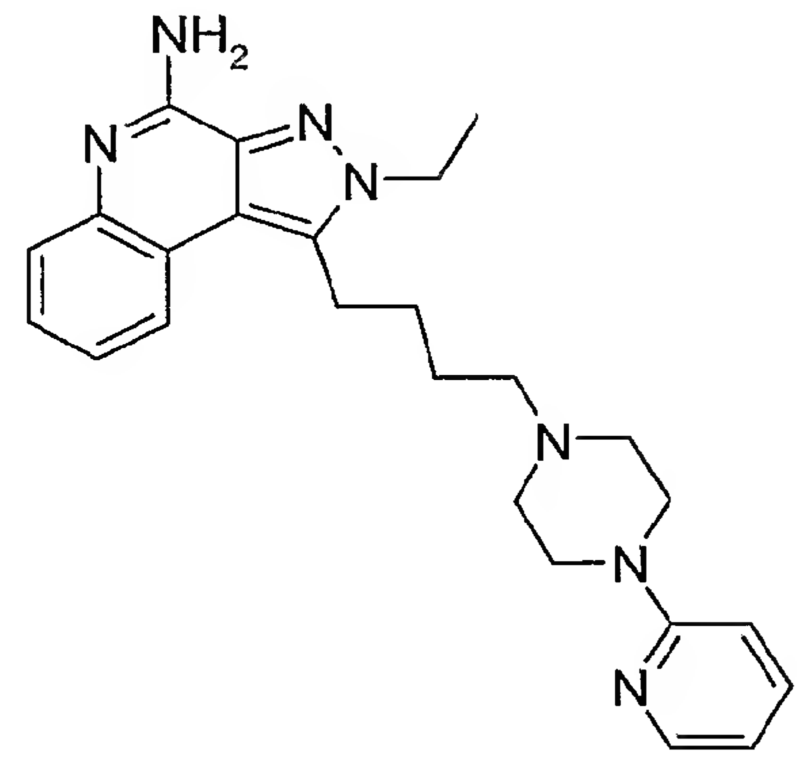
The material from Part G was dissolved in ethanol (20 mL) and a solution of hydrogen chloride in ethanol (4 M, 2.8 mL, 11 mmol) was added. The solution was heated at reflux for 2 hours. Upon cooling to ambient temperature, the solution was concentrated under reduced pressure. To the resulting oil was added 2 M aqueous sodium carbonate until the pH was basic, then brine was added and the mixture was extracted with chloroform. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-30% CMA in chloroform) then was recrystallized from acetonitrile to yield 0.2 g of 1-(4-amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol as light tan crystals, mp 223-225 °C.

MS (APCI) *m/z* 285 $(M + H)^+$;

Anal. calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.38; H, 7.39; N, 19.94.

Example 63

2-Ethyl-1-[4-(4-pyridin-2-ylpiperazin-1-yl)butyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



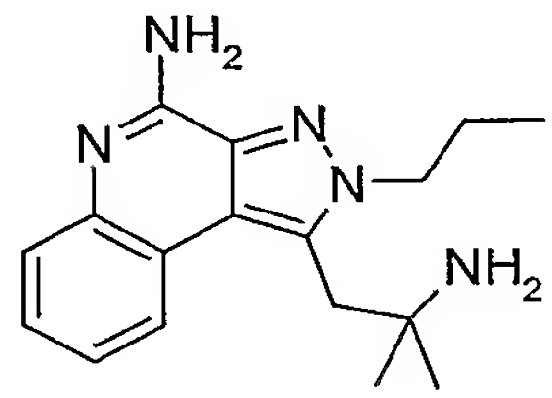
A mixture of 1-(4-chlorobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine (prepared as described in Example 19, 1.0 g, 3.3 mmol), 1-(2-pyridyl)piperazine (0.752 mL, 4.95 mmol), potassium carbonate (1.8 g, 13.2 mmol), and sodium iodide (123 mg, 0.825 mmol) in DMF (6 mL) was heated at 60 °C for 1 hour, then at 90 °C for 2 hours. The reaction was allowed to cool to ambient temperature and white solid formed. Water (100 mL) was added to the mixture. The mixture was stirred for 30 min and the solid was isolated by filtration and dried to yield 1.4 g of 2-ethyl-1-[4-(4-pyridin-2-ylpiperazin-1-yl)butyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine monohydrate as a white solid, mp 183-184 °C.

MS (APCI) *m/z* 430 $(M + H)^+$;

Anal. calcd for $C_{25}H_{31}N_7 \cdot H_2O$: C, 67.09; H, 7.43; N, 21.91. Found: C, 66.86; H, 7.66; N, 22.11.

Example 64

1-(2-Amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A neat mixture of *tert*-butyl 1,1-dimethyl-3-oxobutylcarbamate (prepared as described in B. Peschke *et al.*, *Eur. J. Med. Chem.*, 1999, *34*, 363-380, 14.0 g, 65.0 mmol) and diethyl oxalate (9.50 g, 65.0 mmol) was added in one portion, followed by an ethanol rinse (20 mL), to a stirred solution of sodium *tert*-butoxide (6.25 g, 65.0 mmol) in ethanol (46 mL). A precipitate formed immediately. The mixture was stirred for 2 hours, then acetic acid (66.4 mL) was added. The resulting solution was cooled to 10 °C and propylhydrazine oxalate (10.7 g, 65.0 mmol) was added in one portion. The reaction was stirred for 45 minutes and the internal temperature reached 19 °C. The volatiles were removed under reduced pressure and water was added. The mixture was stirred while 2 M aqueous sodium carbonate was added until carbon dioxide evolution ceased. The mixture was extracted three times with *tert*-butyl methyl ether. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to yield 17.9 g of a yellow solid that was recrystallized from hexanes (130 mL). The crystals were isolated by filtration, washed with cold hexanes, and dried to yield 11.68 g of ethyl 5-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl}-1-propyl-1*H*-pyrazole-3-carboxylate as a white solid, mp 109-111 °C. MS (APCI) m/z 354 $(M + H)^+$; Anal. cacld for $C_{18}H_{31}N_3O_4$: C, 61.17; H, 8.84; N, 11.89. Found: C, 61.18; H, 9.17; N, 11.97.

Part B

Methanol (39.9 mL), lithium hydroxide (5.06 g, 121 mmol), and water (13.3 mL) were added to ethyl 5-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl}-1-propyl-1*H*-pyrazole-3-carboxylate (10.65 g, 30.1 mmol) in a 500 mL round bottom flask. The mixture was stirred vigorously for 5.5 hours. Acetic acid (8.0 mL) and water (200 mL) were added. A white solid formed and more acetic acid (61 mL) was added. The solid was isolated by filtration, washed with water, and dried. A second crop of solid was

isolated from the filtrate. The crops were combined to yield 8.77 g of 5-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl}-1-propyl-1*H*-pyrazole-3-carboxylic acid as a white solid, mp 151-152 °C. MS (APCI) m/z 326 $(M + H)^+$; Anal. calcd for $C_{16}H_{27}N_3O_4$: C, 59.06; H, 8.36; N, 12.91. Found: C, 58.93; H, 8.59; N, 12.94.

Part C

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.68 g, 29.6 mmol) was added to a solution of 5-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl}-1-propyl-1*H*-pyrazole-3-carboxylic acid (8.77 g, 27.0 mmol) and 1-hydroxybenzotriazole (4.00 g, 29.6 mmol) in DMF (44 mL) at ambient temperature. The mixture was stirred for 5.5 hours until a solution formed, then was cooled in an ice bath. Concentrated ammonium hydroxide (5.5 mL) was added and the cloudy solution was stirred for 10 minutes, then was allowed to warm to ambient temperature and stir overnight. Water (150 mL) was added and the mixture was extracted with chloroform (4 x 75 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was concentrated twice from xylene under reduced pressure to afford an oil that was purified on chromatography on a HORIZON HPFC system (silica gel, elution with ethyl acetate) to yield 8.21 g of *tert*-butyl 2-[3-(aminocarbonyl)-1-propyl-1*H*-pyrazol-5-yl]-1,1-dimethylethylcarbamate as a white solid.

Part D

A solution of trifluoroacetic anhydride (3.93 mL, 27.8 mmol) in dichloromethane (51 mL) was added slowly to a 0 °C solution of *tert*-butyl 2-[3-(aminocarbonyl)-1-propyl-1*H*-pyrazol-5-yl]-1,1-dimethylethylcarbamate (8.21 g, 25.3 mmol) and triethylamine (10.6 mL, 75.9 mmol) in dichloromethane (51 mL). After the addition was complete, the cooling bath was removed and the solution was stirred for 90 minutes. The solution was transferred to a separatory funnel and washed with 2 M aqueous sodium carbonate (200 mL). The aqueous layer was extracted twice with chloroform. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield an off white solid that was recrystallized from 10% ethyl acetate in hexanes, isolated by filtration, and dried to yield 6.77 g of *tert*-butyl 2-(3-cyano-1-propyl-1*H*-pyrazol-5-yl)-1,1-dimethylethylcarbamate as a white crystals, mp 115-116 °C. MS (ESI)

m/z 307 $(M + H)^+$; Anal. Calcd for $C_{16}H_{26}N_4O_2$: C, 62.72; H, 8.55; N, 18.28. Found: C, 62.61; H, 8.46; N, 18.52.

Part E

tert-Butyl 2-(3-cyano-1-propyl-1*H*-pyrazol-5-yl)-1,1-dimethylethylcarbamate (5.15 g, 16.8 mmol) was brominated using a modified version of the method described in Part F of Examples 1-4. In the reaction, 1.4 equivalents of bromine were used instead of 1.1 equivalents, chloroform was used instead of dichloromethane in the work-up, and no chromatographic purification was performed. The product, *tert*-butyl 2-(4-bromo-3-cyano-1-propyl-1*H*-pyrazol-5-yl)-1,1-dimethylethylcarbamate (6.97 g), was isolated as a clear, colorless oil that may have contained some chloroform.

Part F

The material from Part E (approximately 16.8 mmol) was dissolved in 1-propanol and concentrated under reduced pressure twice, then was diluted with approximately 29 mL of 1-propanol. To the resulting solution was added 2 M aqueous sodium carbonate (25.2 mL, 50.4 mmol), then water (5.88 mL), triphenylphosphine (397 mg, 1.51 mmol), palladium (II) acetate (113 mg, 0.504 mmol), and 2-aminophenylboronic acid hydrochloride (4.37 g, 25.2 mmol). The flask was equipped with a reflux condenser with a nitrogen inlet and was placed under vacuum and back-filled with nitrogen four times. The reaction was heated under a nitrogen atmosphere at 100 °C for 8 hours. The reaction was allowed to cool to ambient temperature and tetrakis(triphenylphosphine)palladium(0) (388 mg), 2 M aqueous sodium carbonate (25.2 mL), and 2-aminophenylboronic acid hydrochloride (4.37 g) were added. The mixture was heated at 100 °C for 11 hours. The reaction was allowed to cool to ambient temperature, then was extracted with chloroform four times. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to yield a brown oil. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 40-50% ethyl acetate in hexanes followed by 20% CMA in chloroform). The appropriate fractions were combined and concentrated to yield an oil that was purified again by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 35-40% ethyl acetate in hexanes) to afford 2.65 g of a light brown oil.

Part G

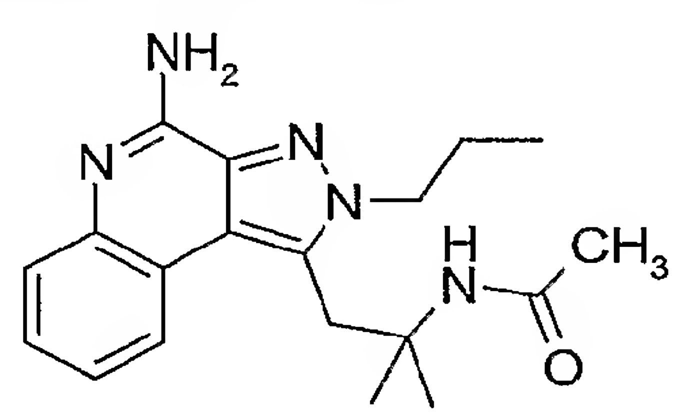
A solution of the material from Part F in 1 M HCl in ethanol (50 mL) was heated at reflux for 3 hours, then was allowed to stand at ambient temperature overnight before being concentrated under reduced pressure to yield a solid suspended in ethanol (approximately 5 mL). The suspension was cooled in an ice bath and diethyl ether (75 mL) was added. The solid was collected by filtration, washed with diethyl ether, and dried to yield 2.3 g of a white solid. The solid was dissolved in water and 2 M aqueous sodium carbonate was added. The mixture was extracted with chloroform five times. The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a white solid that was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 20-30% CMA in chloroform). The appropriate fractions were combined and concentrated to a volume of a few mL. A solid was precipitated with hexanes and was isolated by filtration and dried. The white powder was recrystallized form aceonitrile to yield 1.17 g of 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as white granular crystals, mp 193-195 °C.

MS (APCI) m/z 298 $(M + H)^+$;

Anal. Calcd for $C_{17}H_{23}N_5$: C, 68.66; H, 7.80; N, 23.55. Found: C, 68.59; H, 7.50; N, 23.30.

Example 65

N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]acetamide



Acetyl chloride (221 µL, 3.14 mmol) was added to a 0 °C stirred solution of 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 840 mg, 2.82 mmol) and triethylamine (591 µL, 4.24 mmol) in dichloromethane (25.2 mL). The solution was stirred for 20.5 h at ambient temperature, then was concentrated under reduced pressure to yield a foam that was dissolved in methanol. To the solution was added concentrated hydrochloric acid (2 mL). The solution was stirred at ambient temperature for 90 minutes, then heated at reflux for 40 minutes.

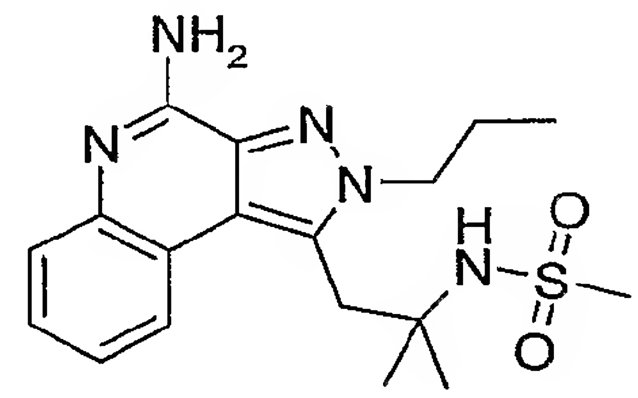
After cooling to ambient temperature, the solution was concentrated under reduced pressure and 2 M aqueous sodium carbonate was added until the pH was basic. The solution was extracted with chloroform. The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in dichlormethane (10 mL), then triethylamine (786 mL) and acetyl chloride (300 mL) were added. The reaction was worked up as before, then methanol (20 mL) and concentrated hydrochloric acid (2 mL) were added. The solution was heated at reflux for 30 minutes, left to stand at ambient temperature overnight, then heated at reflux again for 30 minutes. After cooling to ambient temperature, the solution was concentrated under reduced pressure and 2 M aqueous sodium carbonate was added until the pH was adjusted to pH 10-11. The solution was extracted with chloroform three times. The organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified twice by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 20-30% CMA in chloroform for the first column; gradient elution with 4-10% methanol in chloroform for the second column). The appropriate fractions were combined and concentrated under reduced pressure to yield a colorless foam that was crystallized from ethyl acetate/hexanes. A white solid was isolated and dried under vacuum at elevated temperature to yield 698 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]acetamide as a white solid, mp 182-183 °C.

MS (APCI) m/z 340 $(M + H)^+$;

Anal. Calcd for $C_{19}H_{25}N_5O \cdot 0.25H_2O$: C, 66.35; H, 7.47; N, 20.36. Found: C, 66.29; H, 7.68; N, 20.09.

Example 66

N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide



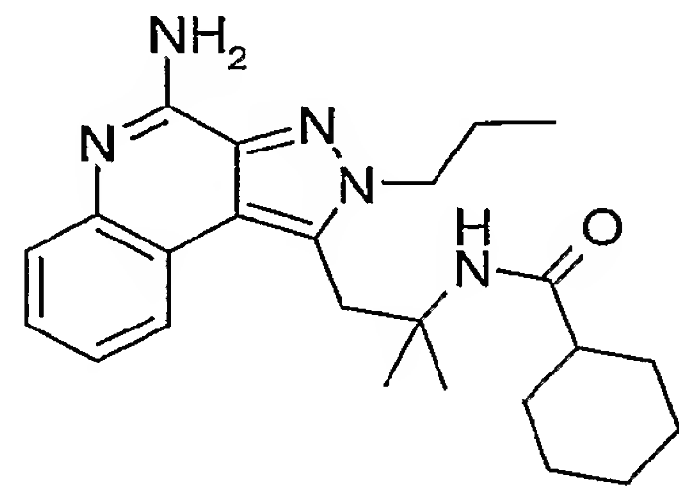
Methanesulfonyl chloride (232 µL, 3.00 mmol) was added to a 0 °C stirred solution of 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 892 mg, 3.00 mmol) and triethylamine (627 µL, 4.5 mmol) in dichloromethane (26.7 mL). After 3 hours at 0 °C, the solution was stirred for 2 days at ambient temperature. To the solution was added 2 M aqueous sodium carbonate. The mixture was extracted with chloroform four times. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a white solid. The crude product was purified by IFC (silica gel, elution with 10% CMA in chloroform). The appropriate fractions were combined and concentrated under reduced pressure to provide a white foam that was crystallized from acetonitrile, isolated by filtration, and dried to yield 600 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide as a white solid, mp 130-139 °C.

MS (APCI) m/z 376 $(M + H)^+$;

Anal. Calcd for $C_{18}H_{25}N_5O_2S \cdot 0.25H_2O$: C, 56.89; H, 6.76; N, 18.43. Found: C, 56.85; H, 7.09; N, 18.40.

Example 67

N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide



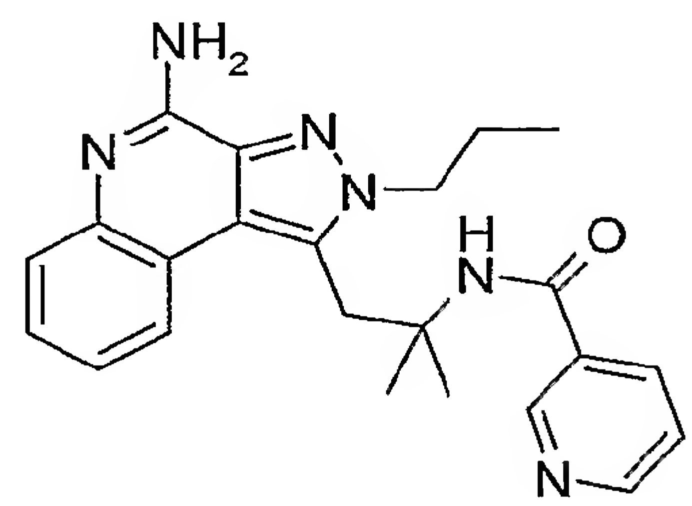
Cyclohexanecarbonyl chloride (401 µL, 3.00 mmol) was added to a 0 °C stirred solution of 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 892 mg, 3.00 mmol) and triethylamine (627 µL, 4.5 mmol) in dichloromethane (26.7 mL). After 3 hours at 0 °C, the solution was stirred for 2 days at ambient temperature. More triethylamine (697 µL) and cyclohexanecarbonyl chloride (602 µL) was added. After 30 minutes, 2 M aqueous sodium carbonate was added to the solution. The mixture was extracted with chloroform four times. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Methanol (20 mL) and concentrated hydrochloric acid (2 mL) were added. The solution was heated at reflux for 4 hours, then left to stand at ambient temperature overnight, then heated at reflux again for brief periods of time during the next 2 days. In all, the solution was heated at reflux for a total of 7 hours. After cooling to ambient temperature, 2 M aqueous sodium carbonate was added to adjust the mixture to pH 10-11. The mixture was concentrated under reduced pressure to remove the methanol. Water was added and a solid was isolated from the mixture by filtration. The solid was washed with water. Chloroform was added to the solid, and the mixture was filtered. The filtrate was concentrated under reduced pressure and purified by IFC. The appropriate fractions were combined and concentrated to a white solid that was recrystallized from 50% ethyl acetate/hexanes. The crystals were isolated by filtration and dried to yield 896 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]cyclohexanecarboxamide as a white solid, mp 190-191 °C.

MS (APCI) m/z 408 $(M + H)^+$;

Anal. Calcd for $C_{24}H_{33}N_5O$: C, 70.73; H, 8.16; N, 17.18. Found: C, 70.58; H, 8.30; N, 16.91.

Example 68

N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]nicotinamide



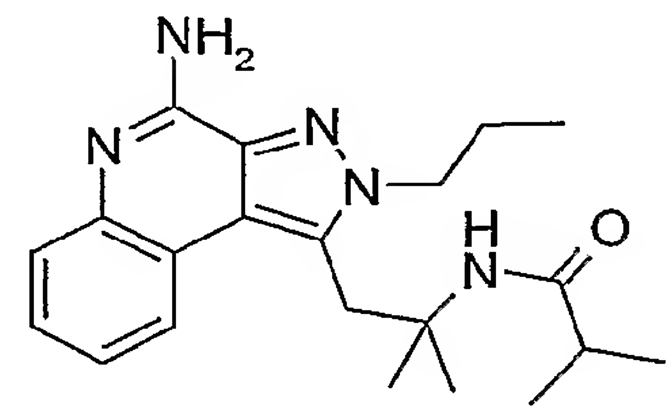
Nicotinoyl chloride hydrochloride (1.62 g, 9.08 mmol) was added to a stirred solution of 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 1.08 g, 3.63 mmol) and triethylamine (2.8 mL, 20 mmol) in dichloromethane (32.4 mL). After 2 h, the solution was concentrated under reduced pressure. The residue was dissolved in methanol (20 mL). Concentrated hydrochloric acid (4 mL) was added and the solution was heated at reflux for 30 minutes, then was allowed to cool to ambient temperature. To the solution was added 2 M aqueous sodium carbonate until the pH was basic, then water was added. The mixture was extracted with chloroform four times. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to yield a brown oil that was purified by IFC (silica gel, elution with CMA in chloroform). The appropriate fractions were combined and concentrated to produce a yellow foam that was crystallized from ethyl acetate/hexanes. The solid was isolated by filtration and dried to yield 418 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]nicotinamide as a pale yellow solid, mp 203-205 °C.

MS (APCI) m/z 403 $(M + H)^+$;

Anal. Calcd for $C_{23}H_{26}N_6O \cdot 1.5H_2O$: C, 64.31; H, 6.80; N, 19.57. Found: C, 64.06; H, 6.56; N, 19.64.

Example 69

N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]-2-methylpropanamide



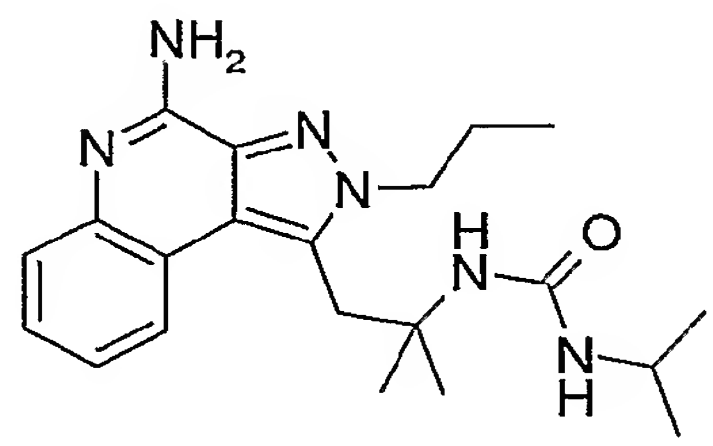
2-Methylpropanoyl chloride (786 µL, 7.50 mmol) was added to a 0 °C stirred solution of 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 892 mg, 3.00 mmol) and triethylamine (1.32 mL, 9.5 mmol) in dichloromethane (26.7 mL). After 10 minutes at 0 °C, the solution was stirred for 2 hours at ambient temperature. The solution was concentrated to afford a white solid that was dissolved in methanol (20 mL) and concentrated hydrochloric acid (4 mL). The solution was heated at reflux for 3.5 hours, then was left to stand at ambient temperature overnight. To the solution was added 2 M aqueous sodium carbonate until the pH was basic. The mixture was concentrated under reduced pressure to remove the methanol. The mixture was extracted with chloroform four times. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to yield an off-white solid that was purified by IFC (silica gel, eluted with CMA in chloroform). The appropriate fractions were combined and concentrated under reduced pressure to yield a white foam that was crystallized from 50% ethyl acetate in hexanes. The solid was isolated by filtration, washed with 50% ethyl acetate in hexanes, and dried to yield 815 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]-2-methylpropanamide as a white solid, mp 177-178.5 °C.

MS (APCI) m/z 368 $(M + H)^+$;

Anal. Calcd for $C_{21}H_{29}N_5O$: C, 68.64; H, 7.95; N, 19.06. Found: C, 68.49; H, 8.23; N, 18.97.

Example 70

N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]-*N'*-isopropylurea



Isopropyl isocyanate (255 mg, 3.00 mmol) was added to a 0 °C stirred solution of 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 892 mg, 3.00 mmol) in dichloromethane (26.7 mL). After 4 hours at 0 °C, the solution was stirred overnight at ambient temperature. The solution was concentrated to afford a colorless resin that was purified by IFC (silica gel, elution with CMA in chloroform). The appropriate fractions were combined and concentrated to yield a solid that was recrystallized from ethyl acetate in hexanes. The solid was isolated by filtration, washed with ethyl acetate/hexanes, and dried to yield 130 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]-*N'*-isopropylurea as a white solid, mp 190-191 °C.

MS (APCI) m/z 383 $(M + H)^+$;

Anal. Calcd for $C_{21}H_{30}N_6O \cdot 0.25H_2O$: C, 65.17; H, 7.94; N, 21.72. Found: C, 65.15; H, 8.03; N, 21.76.

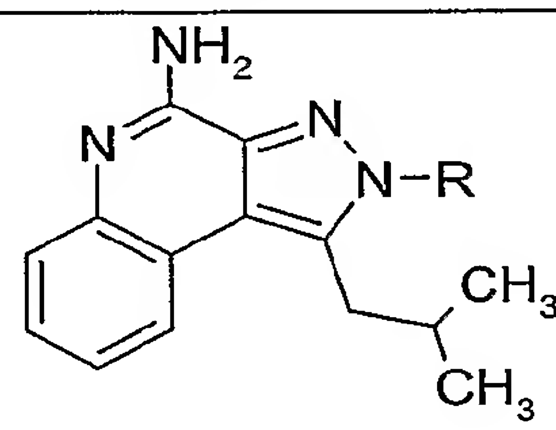
Examples 71-85

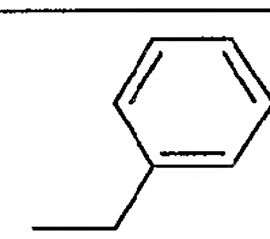
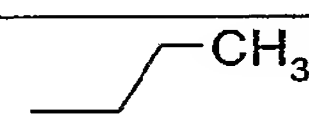
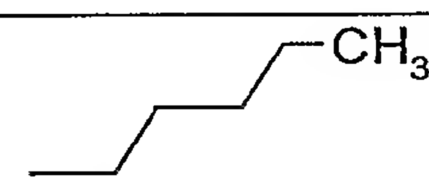
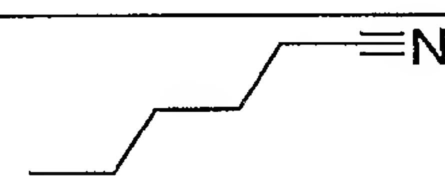
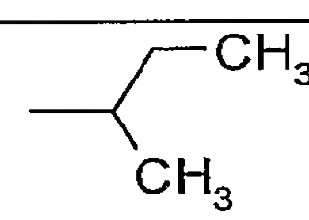
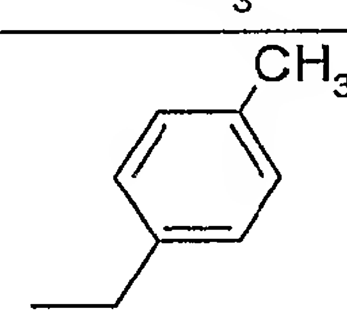
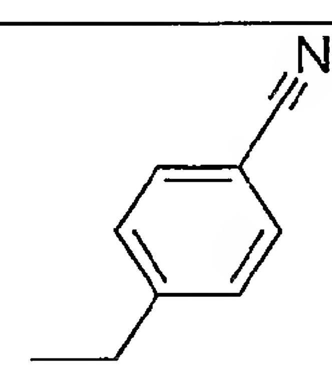
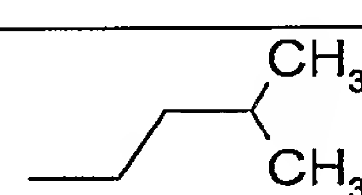
A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 9, 23 mg, 0.10 mmol) and potassium carbonate (approximately 40 mg, 0.29 mmol) in DMF (1 mL). A stirbar was added to each test tube. The test tubes were capped and stirred overnight at ambient temperature. The solvent was removed by vacuum centrifugation.

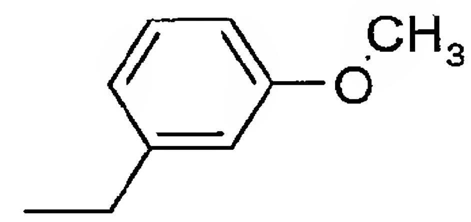
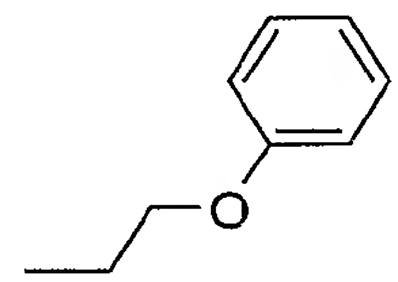
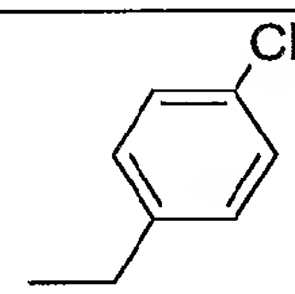
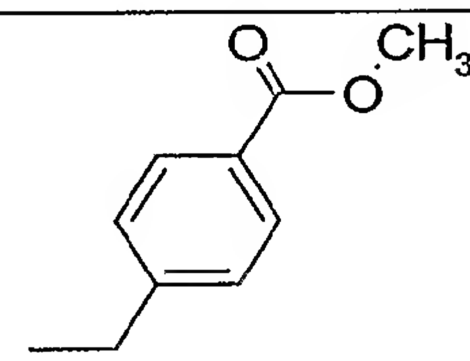
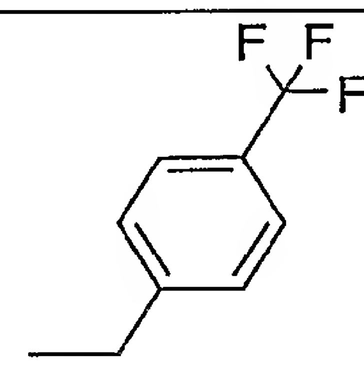
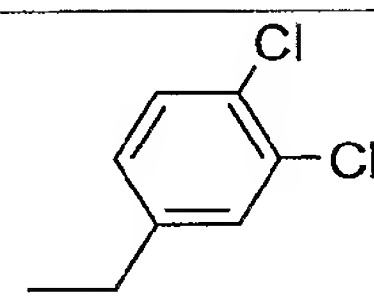
The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate

fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 71-85



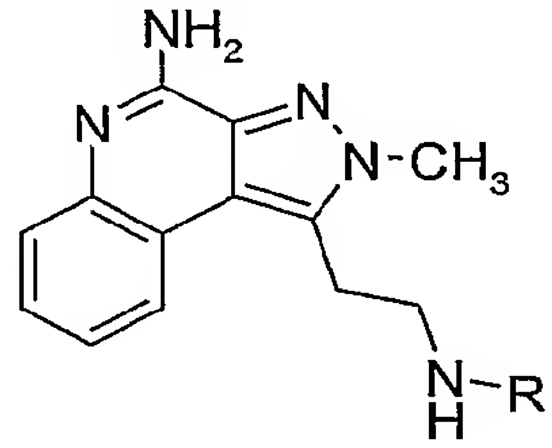
Example	Reagent	R	Measured Mass (M+H)
71	none	—H	241.1455
72	Benzyl bromide		331.1935
73	1-Bromopropane		283.1894
74	1-Bromopentane		311.2221
75	5-Bromovaleronitrile		322.2037
76	2-Iodobutane		297.2060
77	4-Methylbenzyl bromide		345.2080
78	4-Cyanobenzyl bromide		356.1867
79	1-Iodo-3-methylbutane		311.2220

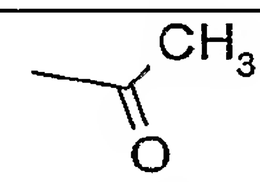
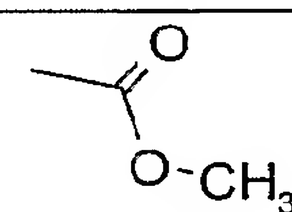
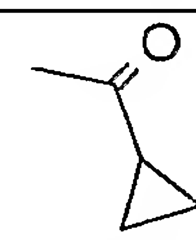
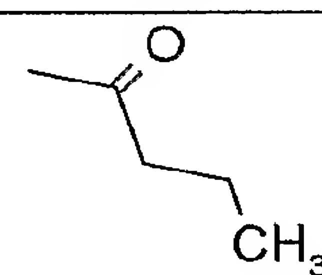
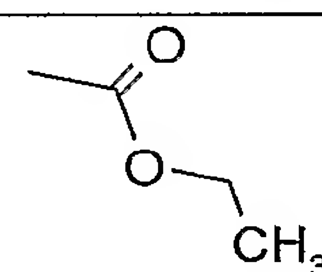
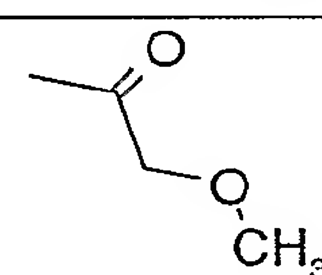
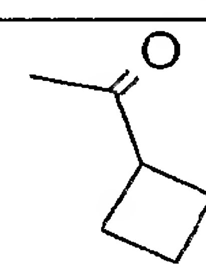
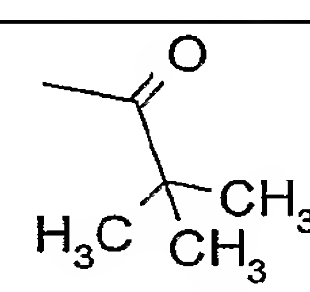
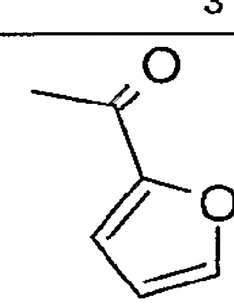
80	3-Methoxybenzyl bromide		361.2035
81	*beta*-Bromophenetole		361.2040
82	4-Chlorobenzyl bromide		365.1545
83	Methyl 4-(bromomethyl)benzoate		389.1986
84	4-(Trifluoromethyl)benzyl bromide		399.1820
85	3,4-Dichlorobenzyl bromide		399.1148

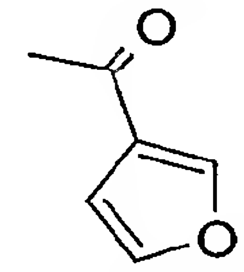
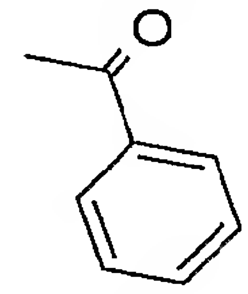
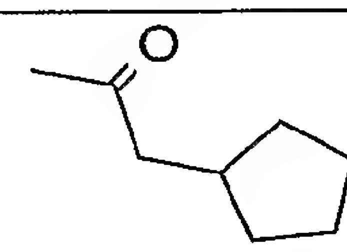
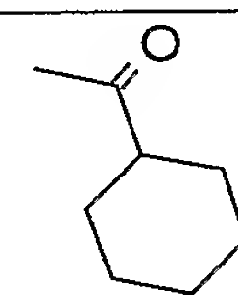
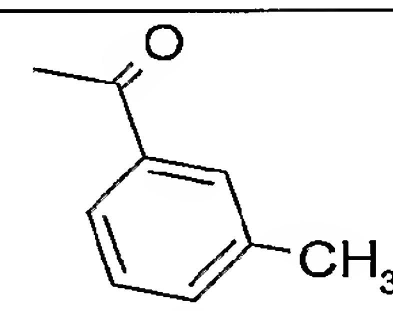
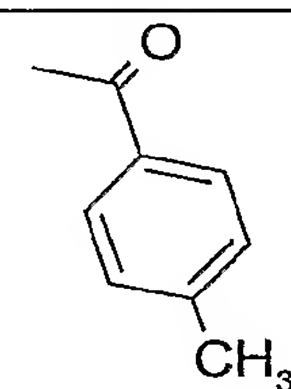
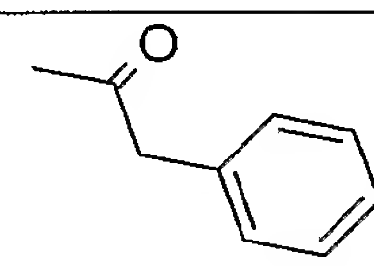
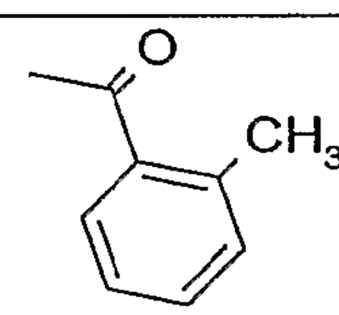
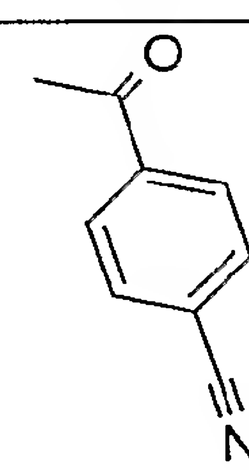
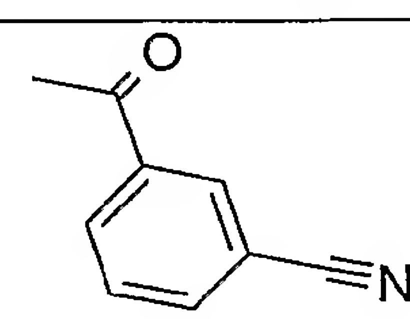
Examples 86-197

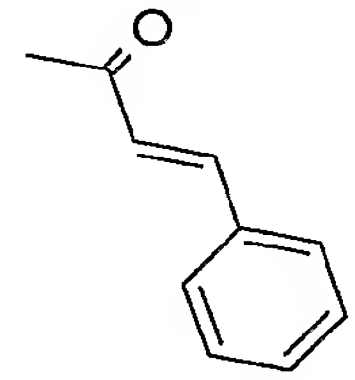
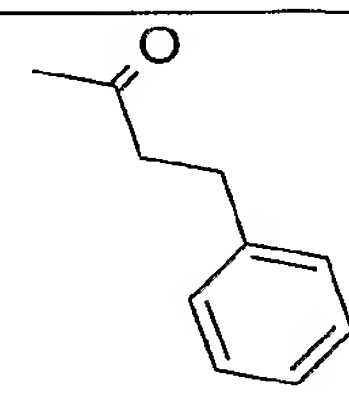
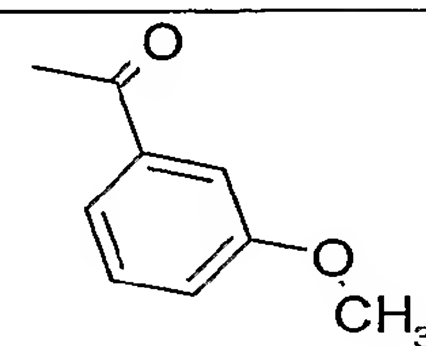
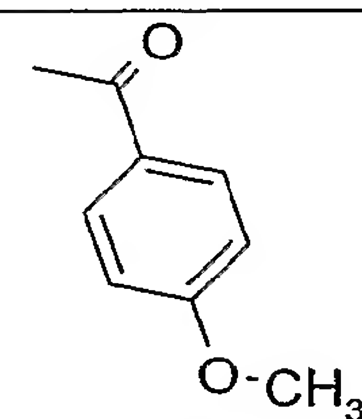
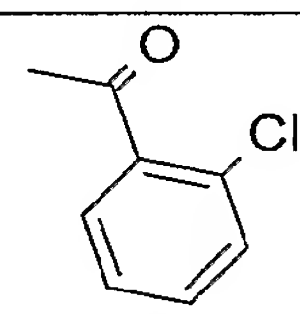
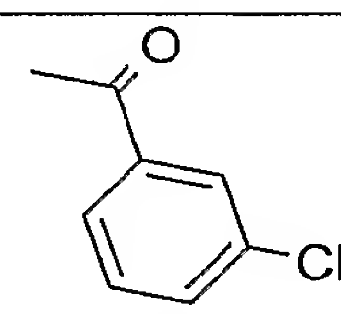
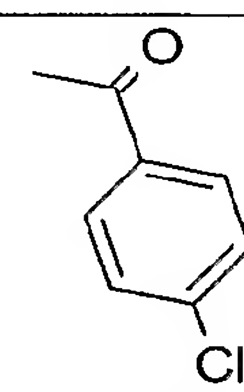
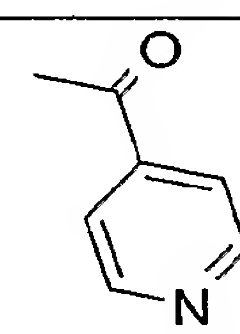
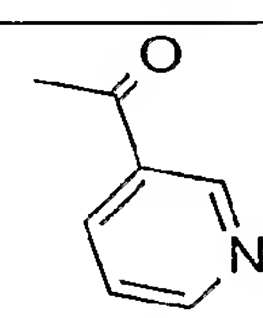
A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(2-aminoethyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride (prepared as described in Parts A-J of Example 50, 31 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.069 mL, 0.40 mmol) in DMF (1 mL). The test tubes were capped, shaken for four hours at ambient temperature. The solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

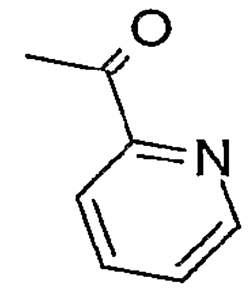
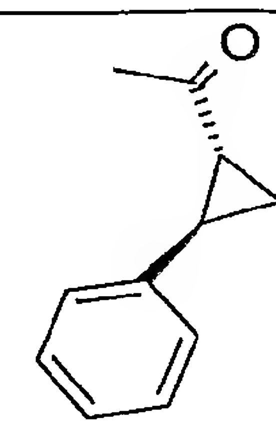
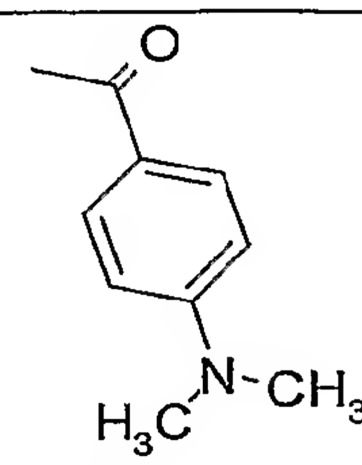
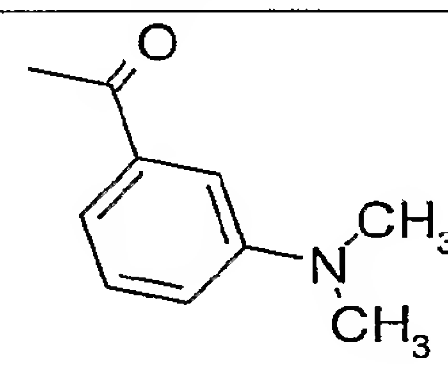
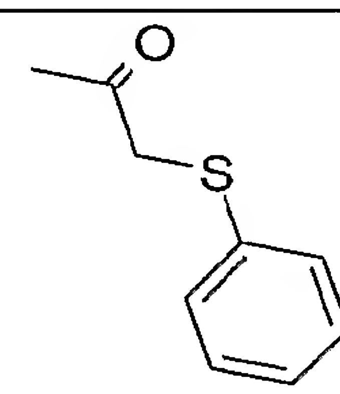
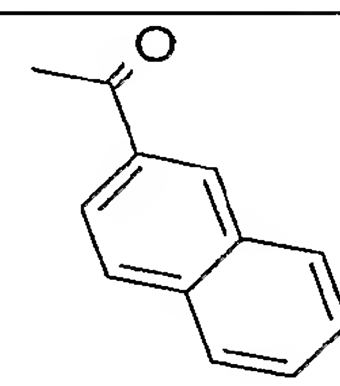
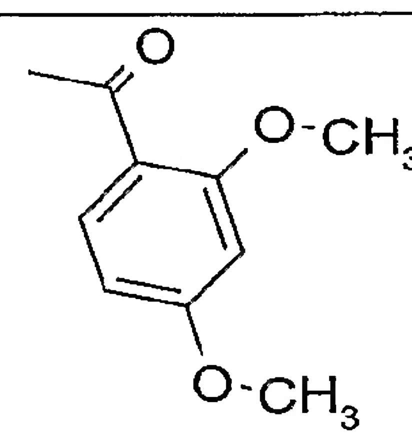
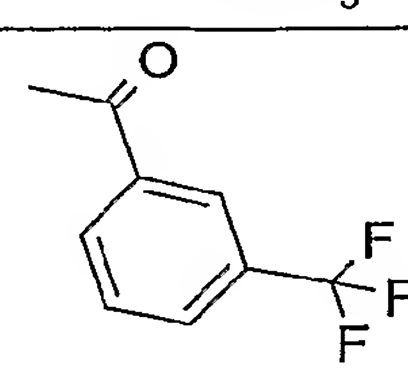
Examples 86-197

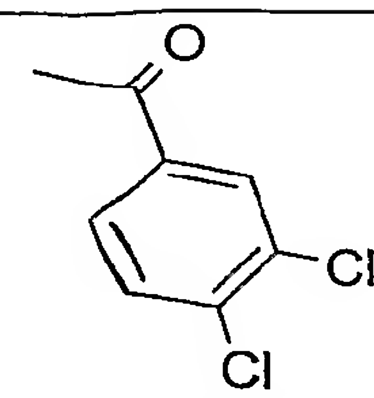
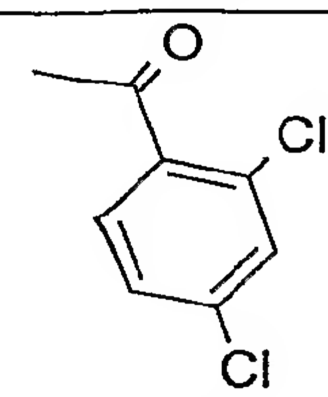
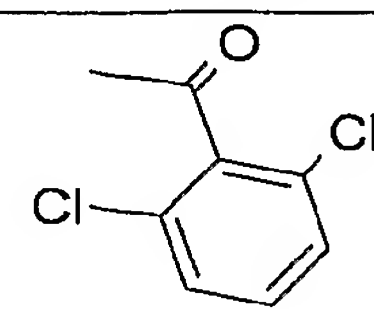
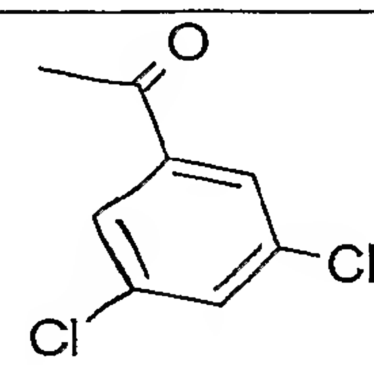
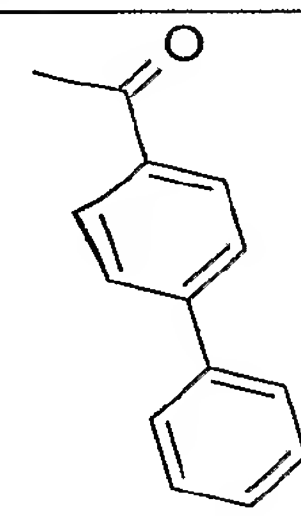
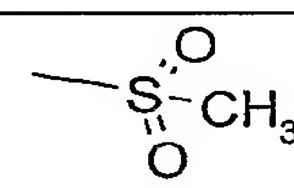
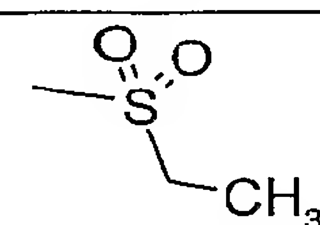
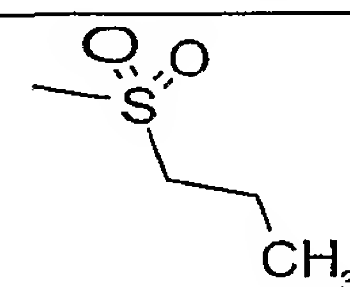
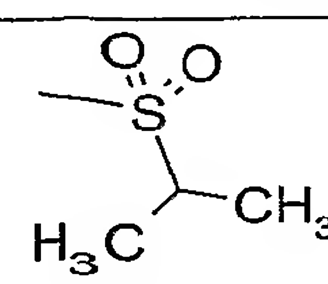
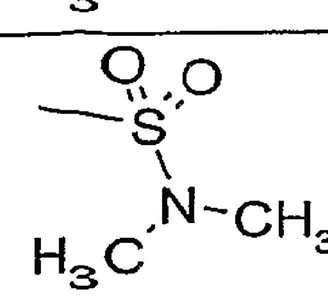


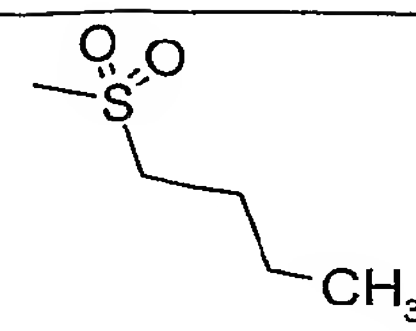
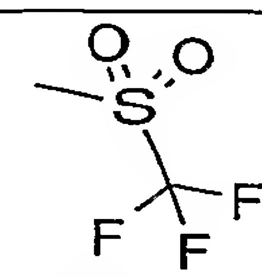
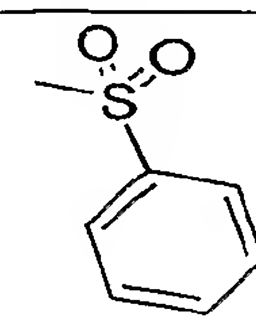
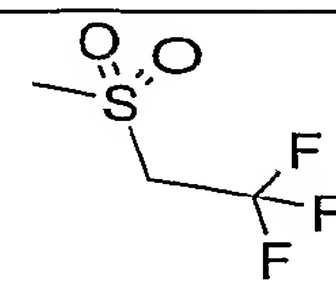
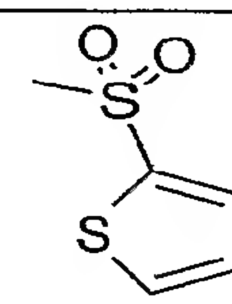
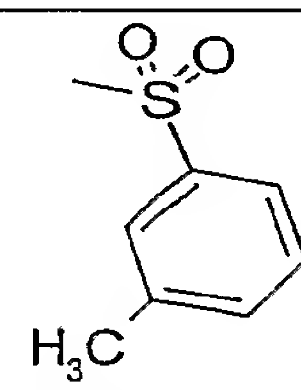
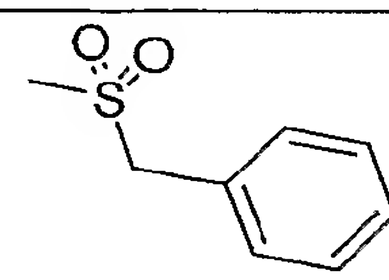
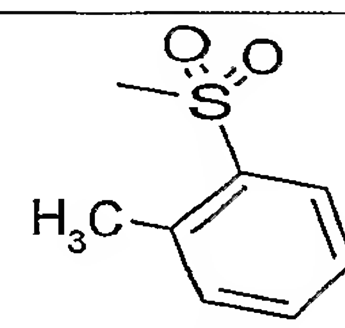
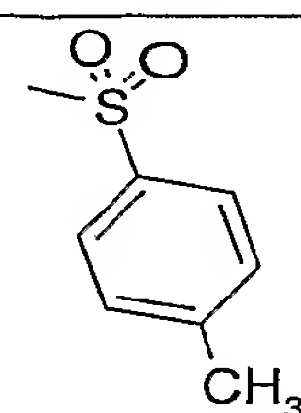
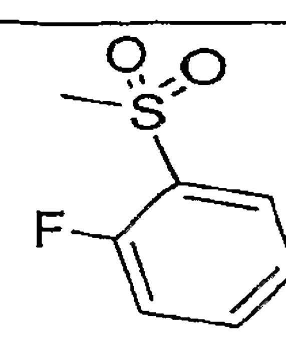
Example	Reagent	R	Measured Mass (M+H)
86	none		242.1400
87	Acetyl chloride		284.1511
88	Methyl chloroformate		300.1460
89	Cyclopropanecarbonyl chloride		310.1672
90	Butryl chloride		312.1812
91	Ethyl chloroformate		314.1607
92	Methoxyacetyl chloride		314.1599
93	Cyclobutanecarbonyl chloride		324.1807
94	Pivaloyl chloride		326.1982
95	2-Furoyl chloride		336.1455

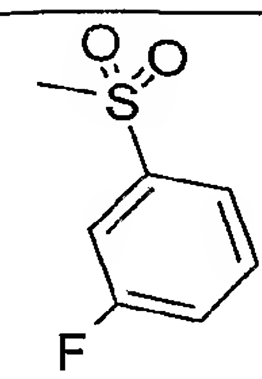
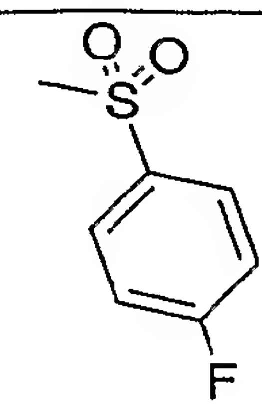
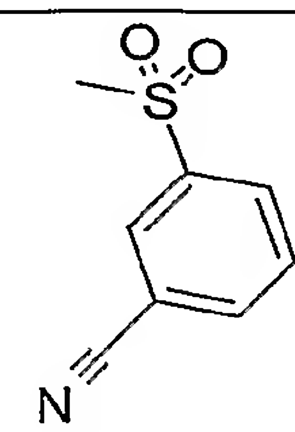
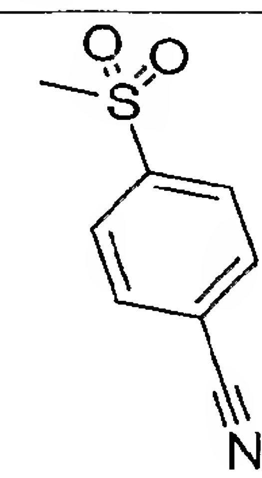
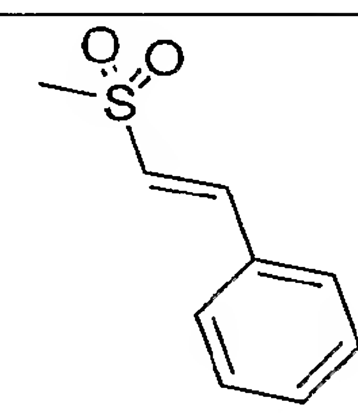
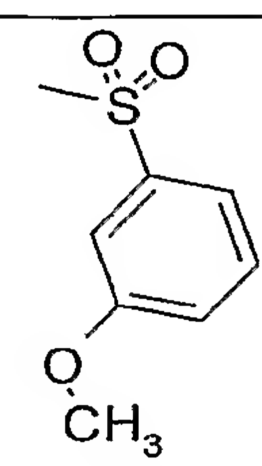
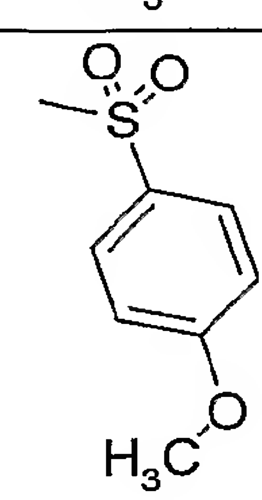
96	3-Furoyl chloride		336.1483
97	Benzoyl chloride		346.1654
98	Cyclopentylacetyl chloride		352.2130
99	Cyclohexanecarbonyl chloride		352.2140
100	*m*-Toluoyl chloride		360.1840
101	*p*-Toluoyl chloride		360.1839
102	Phenylacetyl chloride		360.1836
103	*o*-Toluoyl chloride		360.1823
104	4-Cyanobenzoyl chloride		371.1636
105	3-Cyanobenzoyl chloride		371.1608

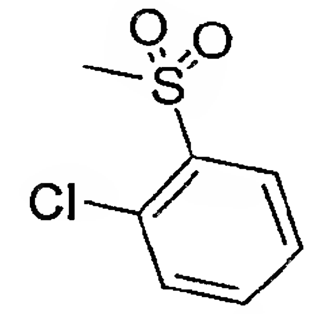
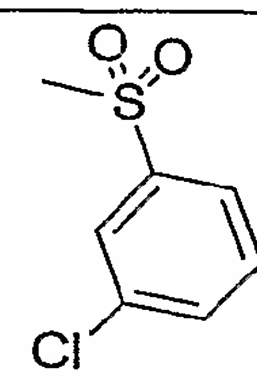
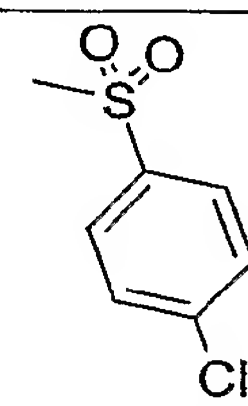
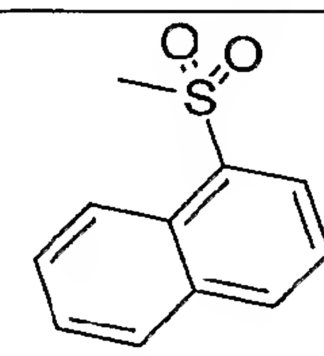
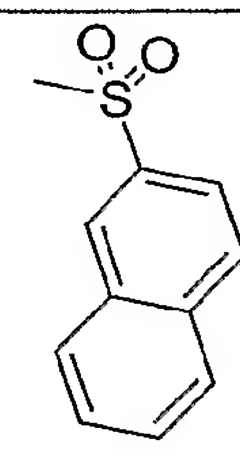
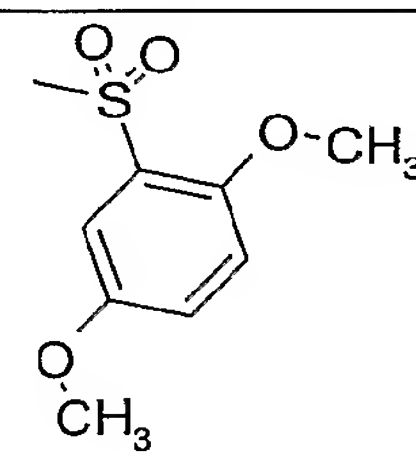
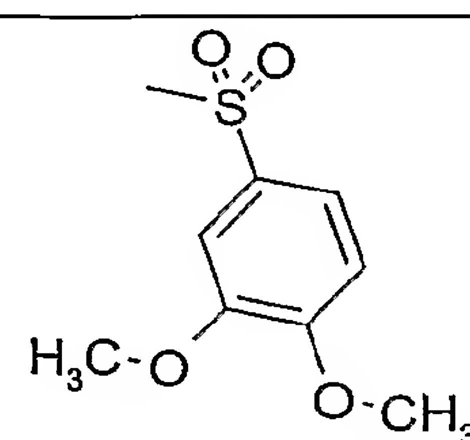
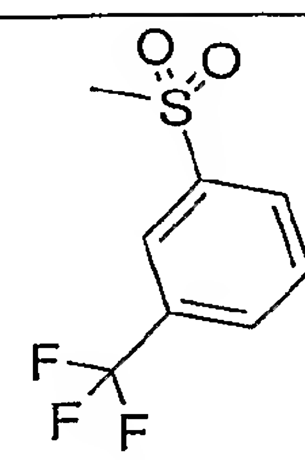
106	Cinnamoyl chloride		372.1824
107	Hydrocinnamoyl chloride		374.1956
108	3-Methoxybenzoyl chloride		376.1795
109	*p*-Anisoyl chloride		376.1804
110	2-Chlorobenzoyl chloride		380.1255
111	3-Chlorobenzoyl chloride		380.1294
112	4-Chlorobenzoyl chloride		380.1310
113	Isonicotinoyl chloride hydrochloride		347.1617
114	Nicotinoyl chloride hydrochloride		347.1597

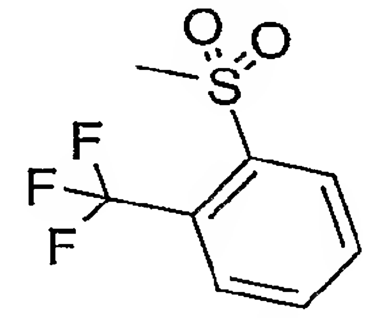
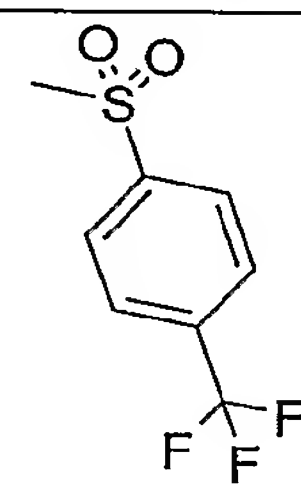
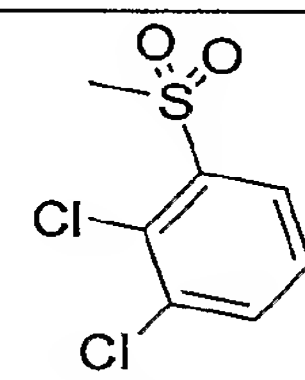
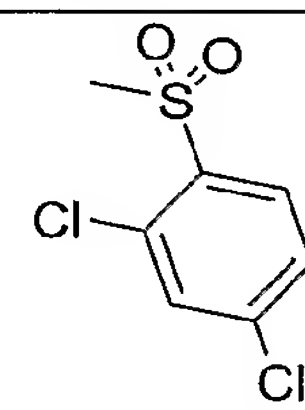
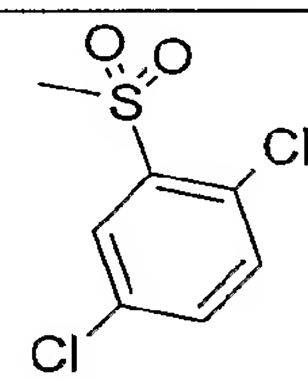
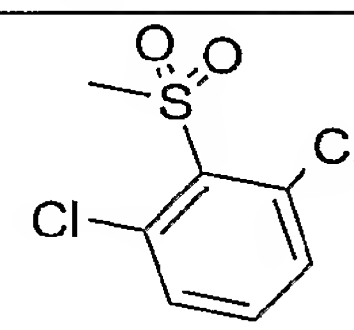
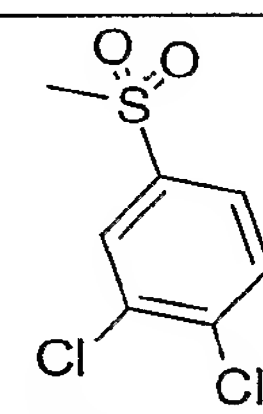
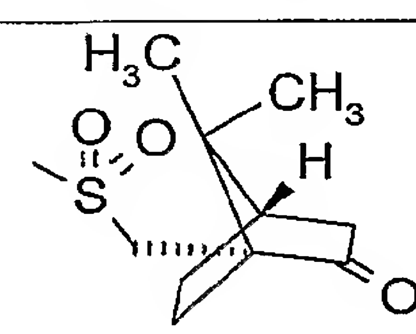
115	Picolinoyl chloride hydrochloride		347.1585
116	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		386.1975
117	4-Dimethylaminobenzoyl chloride		389.2125
118	3-Dimethylaminobenzoyl chloride		389.2104
119	(Phenylthio)acetyl chloride		392.1530
120	2-Naphthoyl chloride		396.1837
121	2,4-Dimethoxybenzoyl chloride		406.1906
122	3-(Trifluoromethyl)benzoyl chloride		414.1536

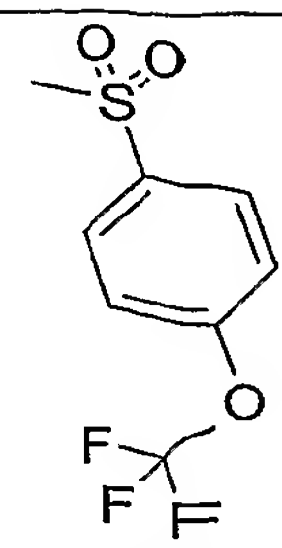
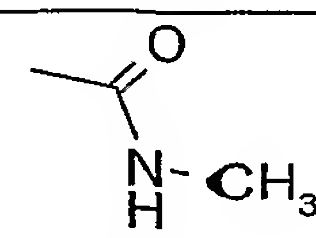
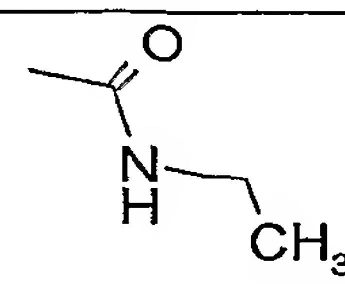
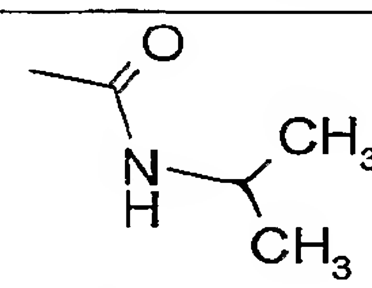
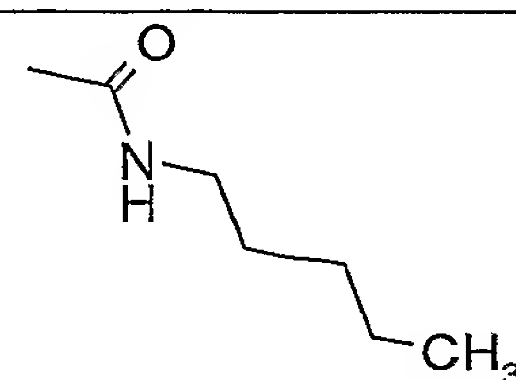
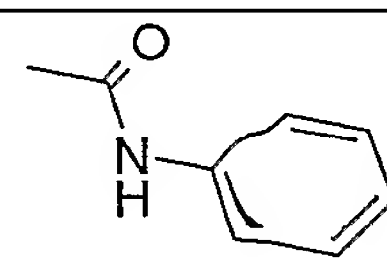
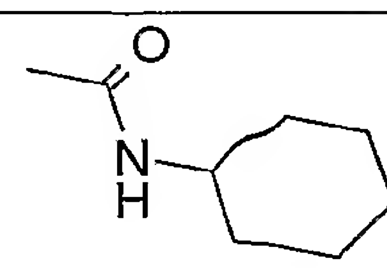
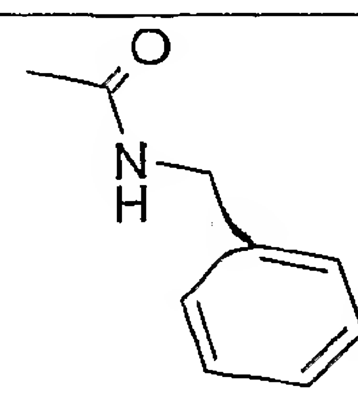
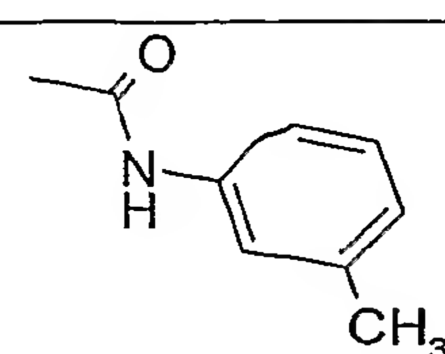
123	3,4-Dichlorobenzoyl chloride		414.0906
124	2,4-Dichlorobenzoyl chloride		414.0908
125	2,6-Dichlorobenzoyl chloride		414.0900
126	3,5-Dichlorobenzoyl chloride		414.0910
127	4-Biphenylcarbonyl chloride		422.2006
128	Methanesulfonyl chloride		320.1184
129	Ethanesulfonyl chloride		334.1332
130	1-Propanesulfonyl chloride		348.1492
131	Isopropylsulfonyl chloride		348.1521
132	Dimethylsulfamoyl chloride		349.1465

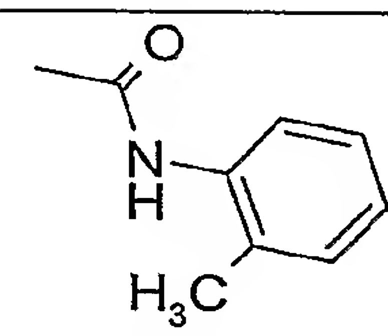
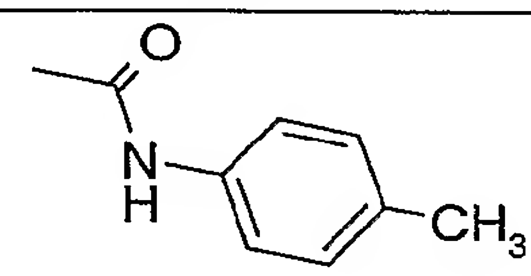
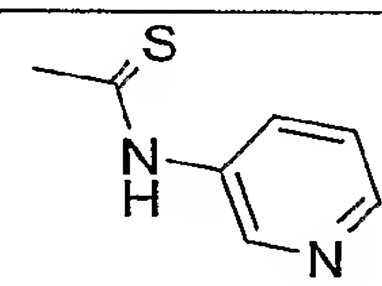
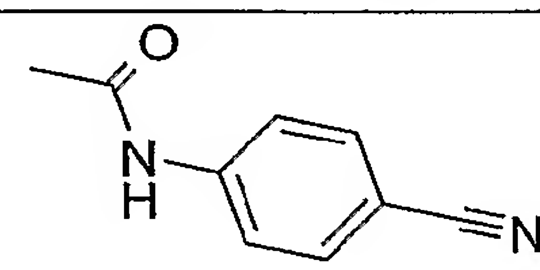
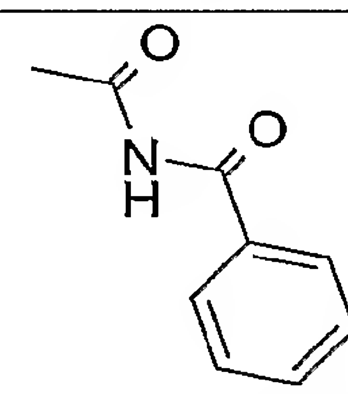
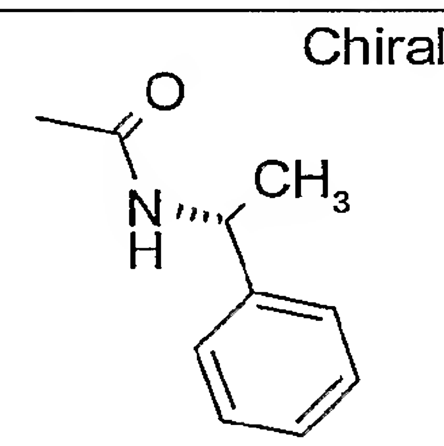
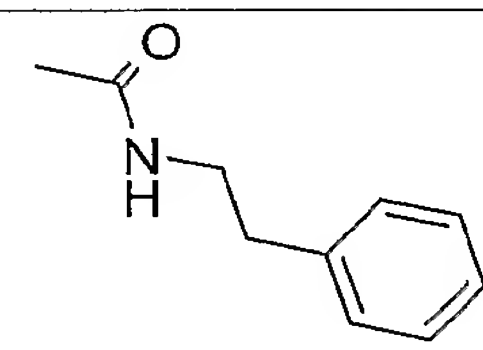
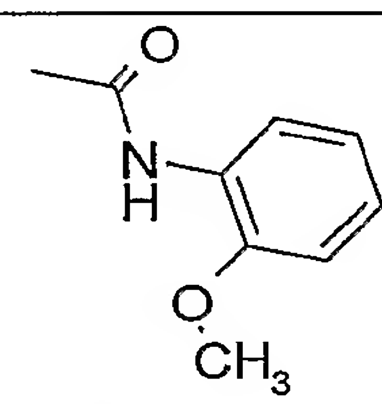
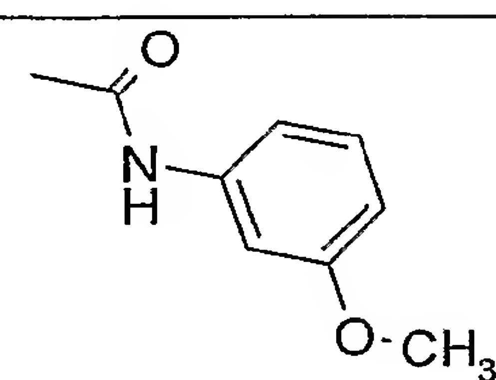
133	1-Butanesulfonyl chloride		362.1653
134	Trifluoromethanesulfonyl chloride		374.0889
135	Benzenesulfonyl chloride		382.1341
136	2,2,2-Trifluoroethanesulfonyl chloride		388.1060
137	2-Thiophenesulfonyl chloride		388.0883
138	3-Methylbenzenesulfonyl chloride		396.1499
139	*alpha*-Toluenesulfonyl chloride		396.1493
140	*o*-Toluenesulfonyl chloride		396.1525
141	*p*-Toluenesulfonyl chloride		396.1475
142	2-Fluorobenzenesulfonyl chloride		400.1256

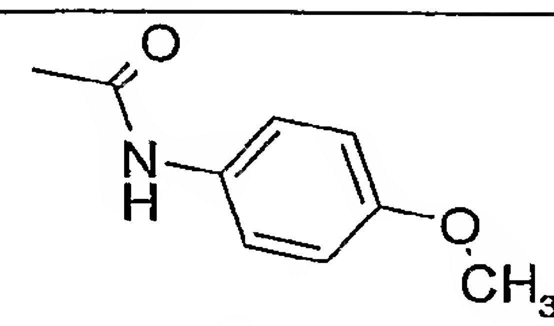
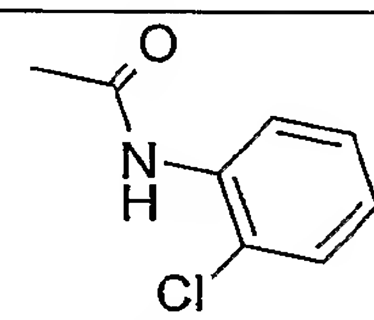
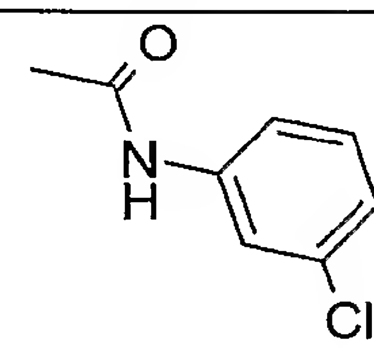
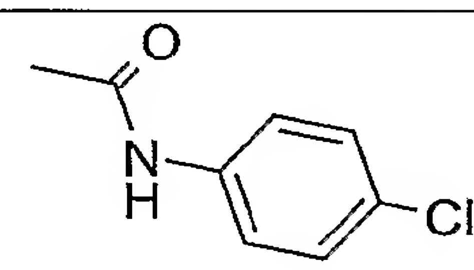
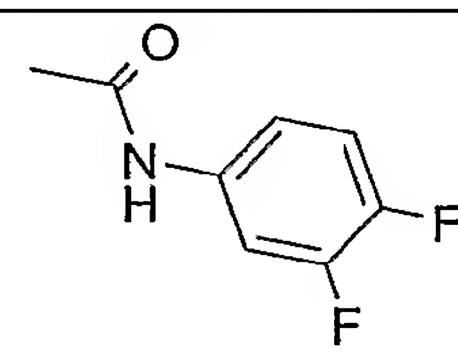
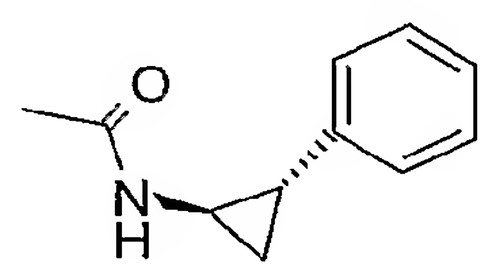
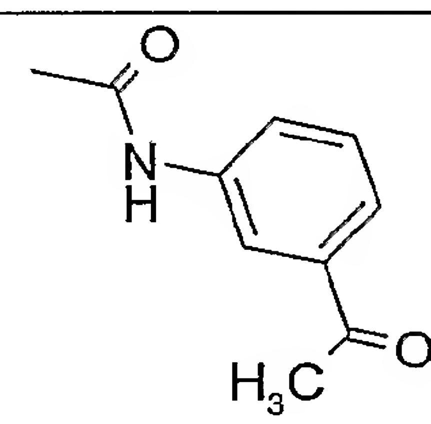
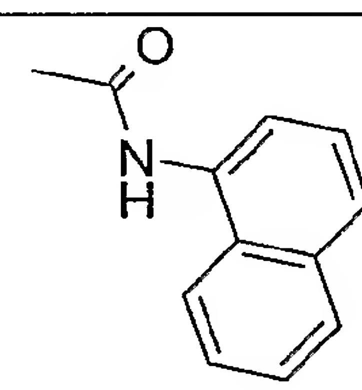
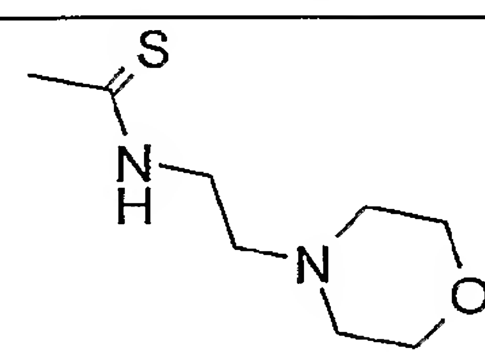
143	3-Fluorobenzenesulfonyl chloride		400.1277
144	4-Fluorobenzenesulfonyl chloride		400.1235
145	3-Cyanobenzenesulfonyl chloride		407.1299
146	4-Cyanobenzenesulfonyl chloride		407.1327
147	*beta*-Styrenesulfonyl chloride		408.1498
148	3-Methoxybenzenesulfonyl chloride		412.1471
149	4-Methoxybenzenesulfonyl chloride		412.1478

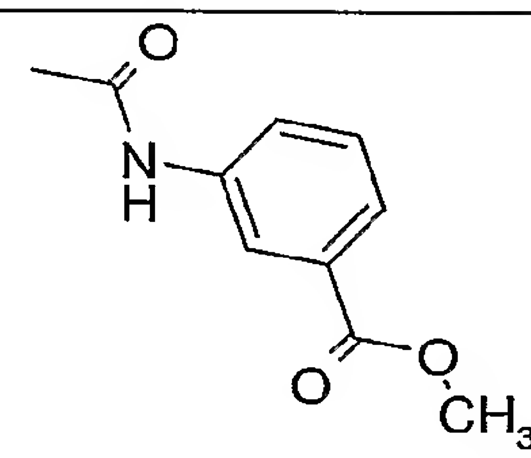
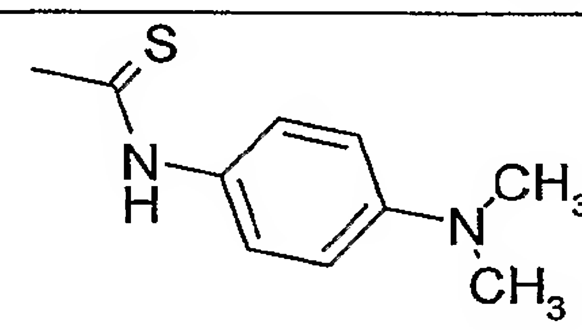
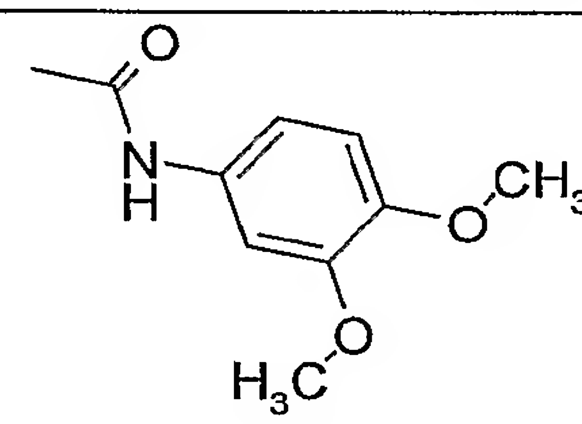
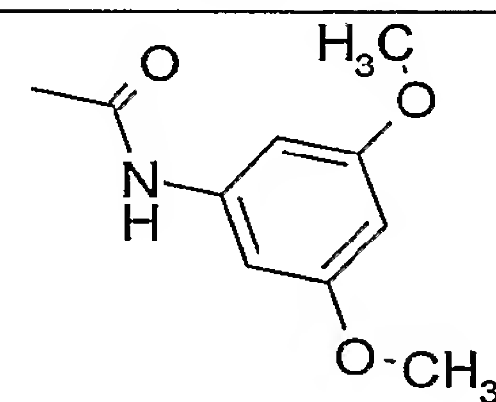
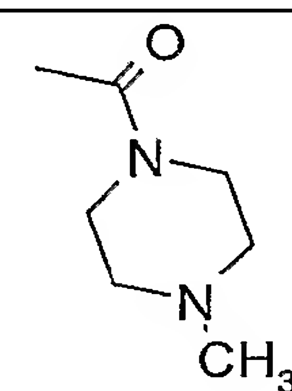
150	2-Chlorobenzenesulfonyl chloride		416.0967
151	3-Chlorobenzenesulfonyl chloride		416.0960
152	4-Chlorobenzenesulfonyl chloride		416.0978
153	1-Naphthalenesulfonyl chloride		432.1494
154	2- Naphthalenesulfonyl chloride		432.1490
155	2,5-Dimethoxybenzenesulfonyl chloride		442.1533
156	3,4- Dimethoxybenzenesulfonyl chloride		442.1549
157	3-(Trifluoromethyl)benzenesulfonyl chloride		450.1183

158	2-(Trifluoromethyl)benzenesulfonyl chloride		450.1194
159	4-(Trifluoromethyl)benzenesulfonyl chloride		450.1187
160	2,3-Dichlorobenzenesulfonyl chloride		450.0583
161	2,4- Dichlorobenzenesulfonyl chloride		450.0587
162	2,5- Dichlorobenzenesulfonyl chloride		450.0571
163	2,6- Dichlorobenzenesulfonyl chloride		450.0598
164	3,4- Dichlorobenzenesulfonyl chloride		450.0583
165	10-Camphorsulfonyl chloride		456.2094

166	4-(Trifluoromethoxy)benzenesulfonyl chloride		466.1161
167	Methyl isocyanate		299.1630
168	Ethyl isocyanate		313.1789
169	Isopropyl isocyanate		327.1940
170	Pentyl isocyanate		355.2246
171	Phenyl isocyanate		361.1775
172	Cyclohexyl isocyanate		367.2263
173	Benzyl isocyanate		375.1959
174	*m*-Tolyl isocyanate		375.1939

175	*o*- Tolyl isocyanate		375.1937
176	*p*- Tolyl isocyanate		375.1939
177	3-Pyridyl isothiocyanate		378.1530
178	4-Cyanophenyl isocyanate		386.1752
179	Benzoyl isocyanate		389.1724
180	(R)-(+)-*alpha*-Methylbenzyl isocyanate		389.2057
181	2-Phenyl ethylisocyanate		389.2061
182	2-Methoxyphenyl isocyanate		391.1881
183	3-Methoxyphenyl isocyanate		391.1856

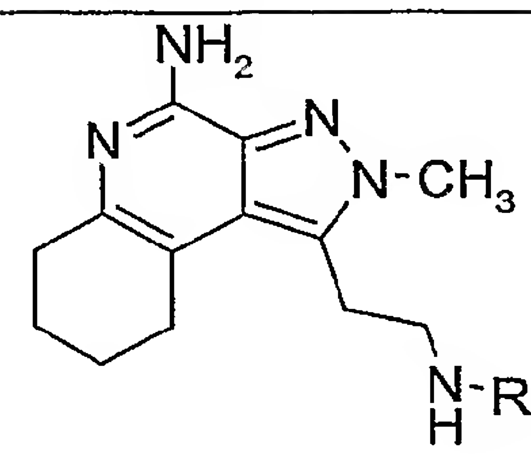
184	4-Methoxyphenyl isocyanate		391.1888
185	2-Chlorophenyl isocyanate		395.1394
186	3-Chlorophenyl isocyanate		395.1395
187	4-Chlorophenyl isocyanate		395.1357
188	3,4-Difluorophenyl isocyanate		397.1572
189	*trans*-2-Phenylcyclopropyl isocyanate		401.2105
190	3-Acetylphenyl isocyanate		403.1882
191	1-Naphthyl isocyanate		411.1963
192	2-Morpholinoethyl isothiocyanate		414.2108

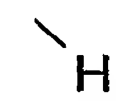
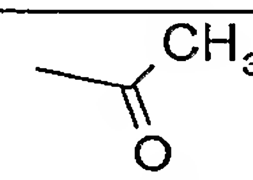
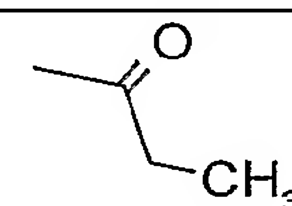
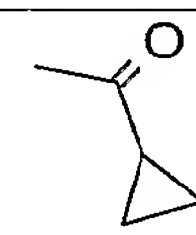
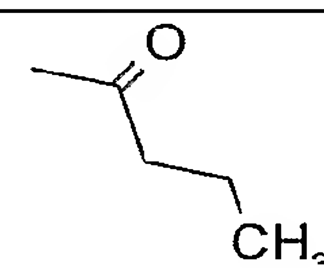
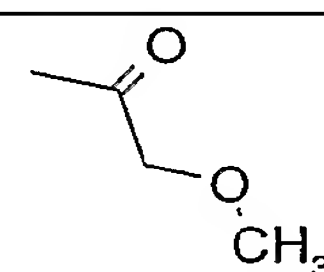
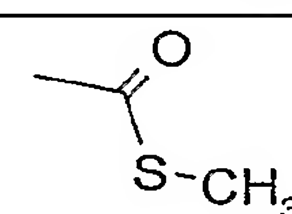
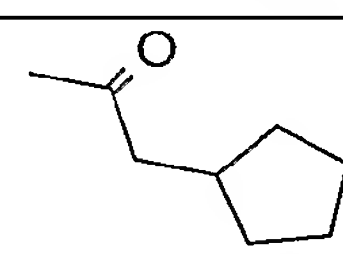
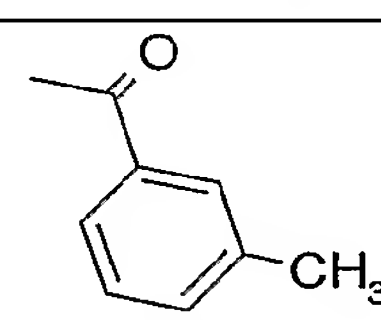
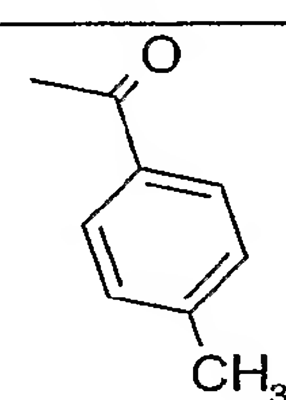
193	3-Carbomethoxyphenyl isocyanate		419.1846
194	4-(Dimethylamino)isothiocyanate		420.1989
195	3,4-Dimethoxyphenyl isocyanate		421.1974
196	3,5- Dimethoxyphenyl isocyanate		421.1998
197	4-Methyl-1-piperazinecarbonyl chloride		368.2194

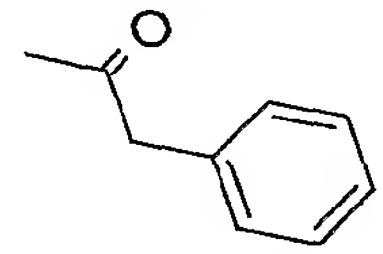
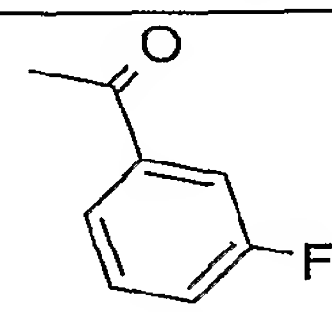
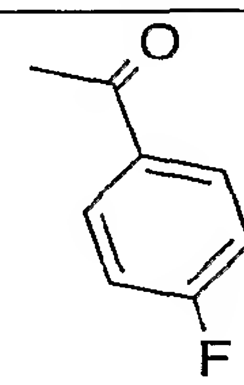
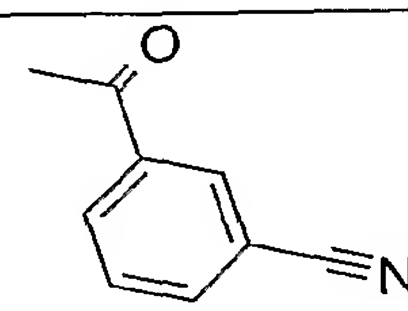
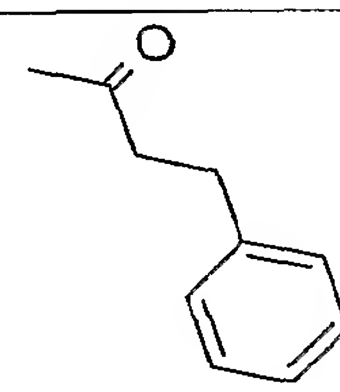
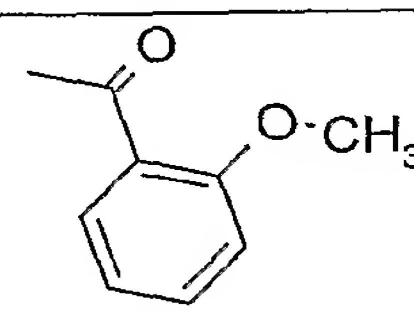
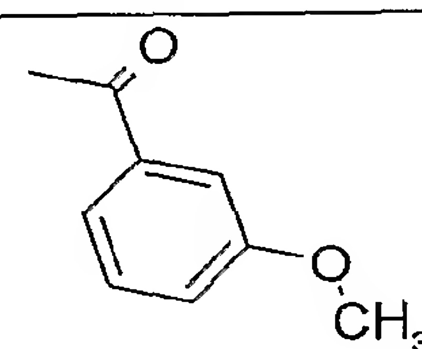
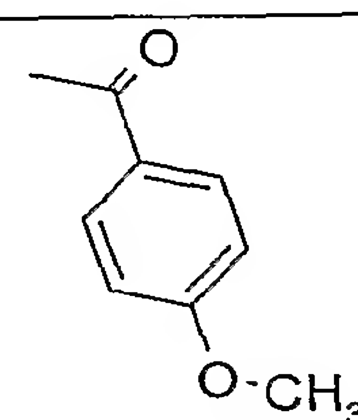
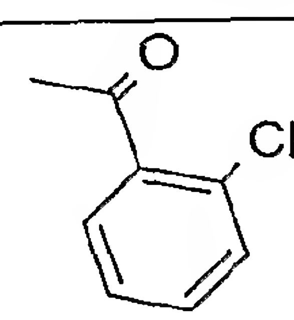
Examples 198-270

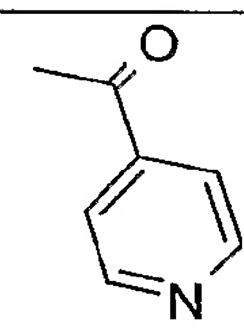
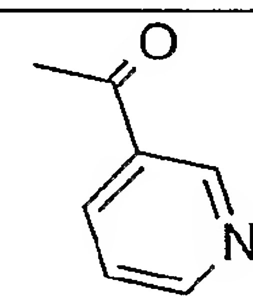
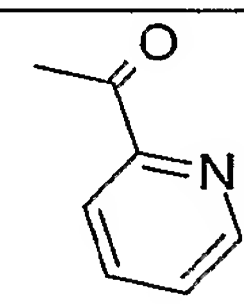
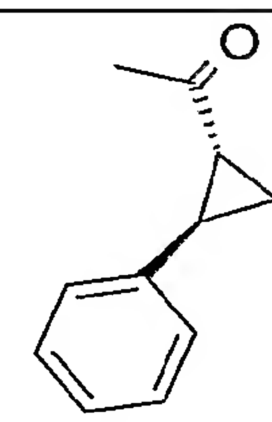
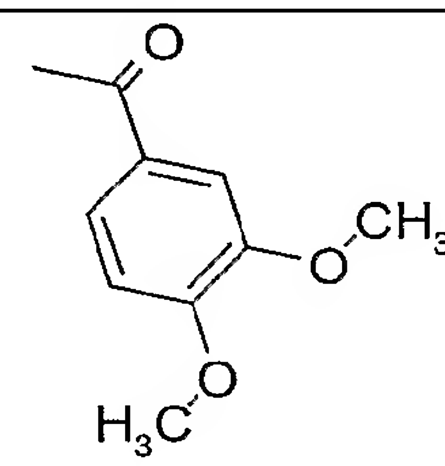
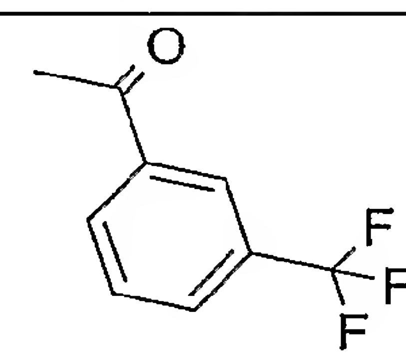
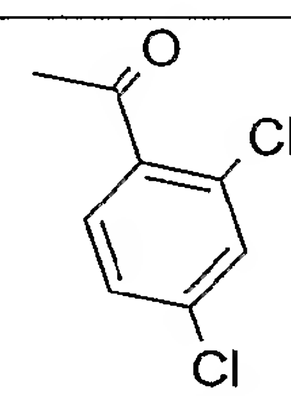
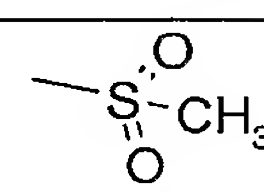
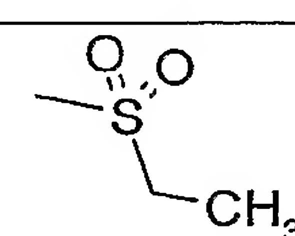
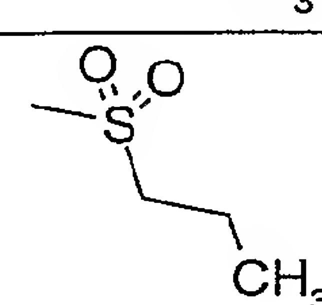
A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(2-aminoethyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 50, 25 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.035 mL, 0.20 mmol) in chloroform (1 mL). The test tubes were capped, shaken for four hours at ambient temperature, and then were shaken overnight. Two drops of water were added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

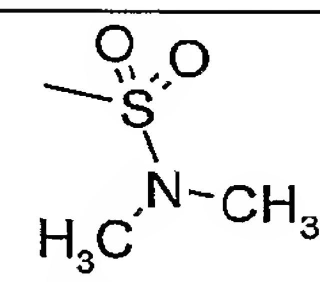
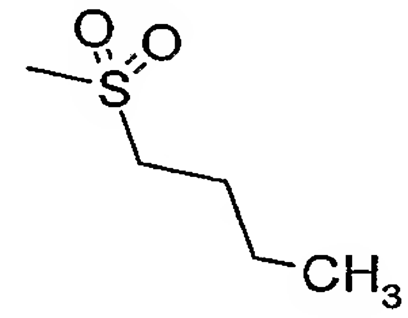
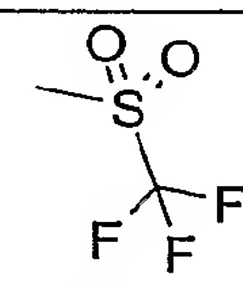
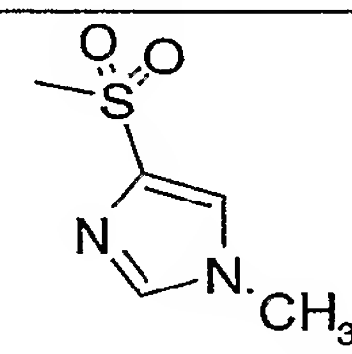
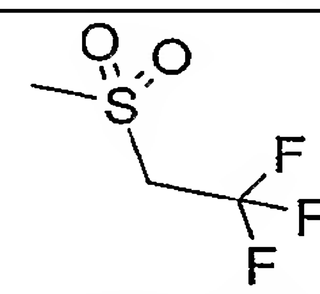
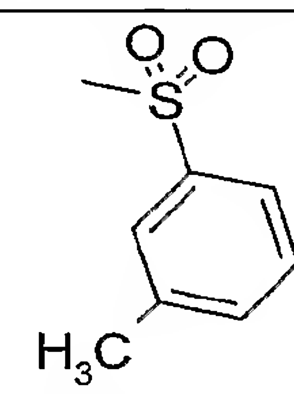
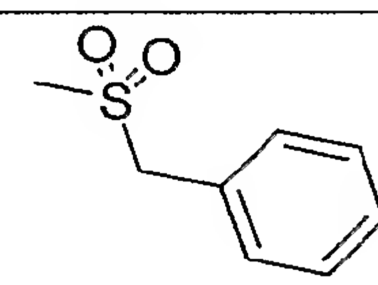
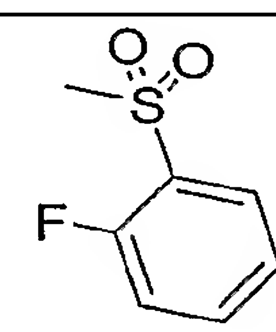
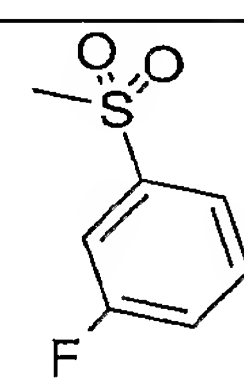
Examples 198-270

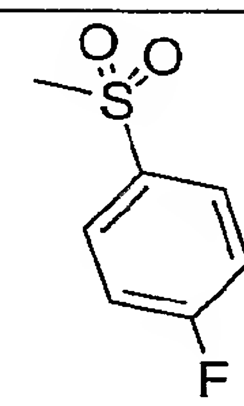
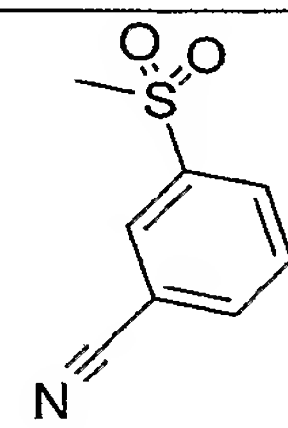
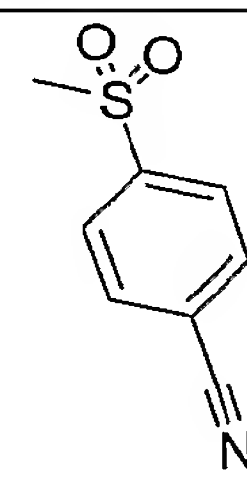
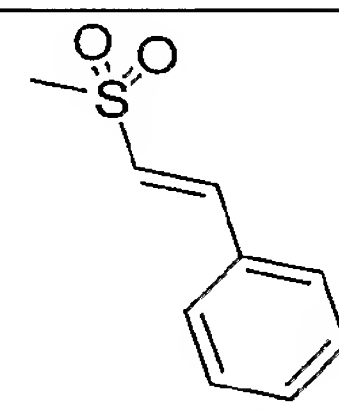
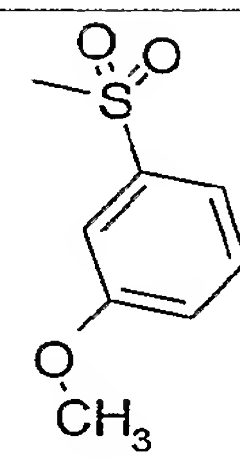
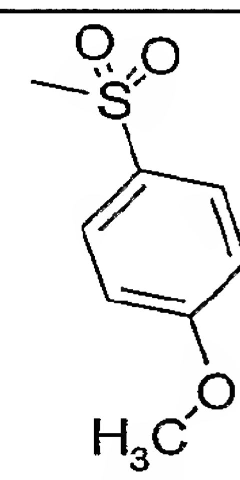
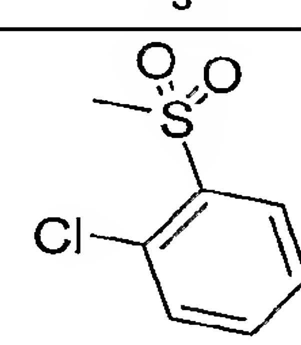


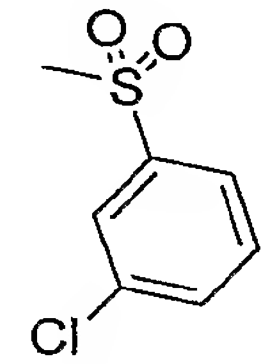
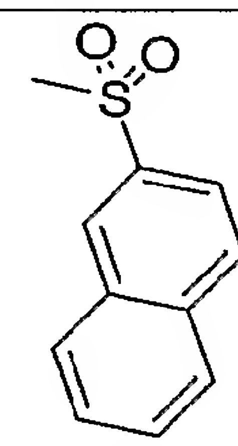
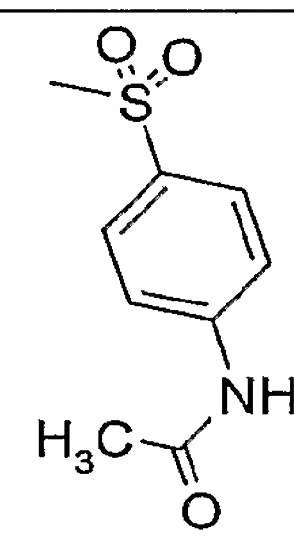
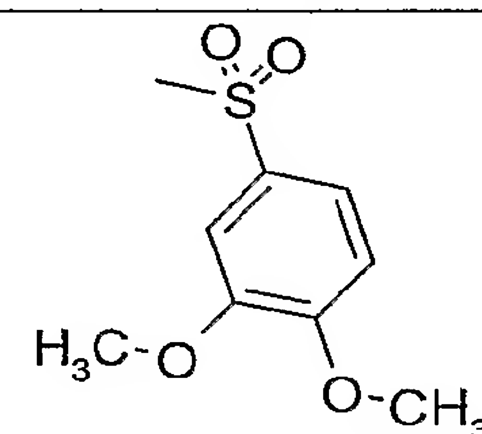
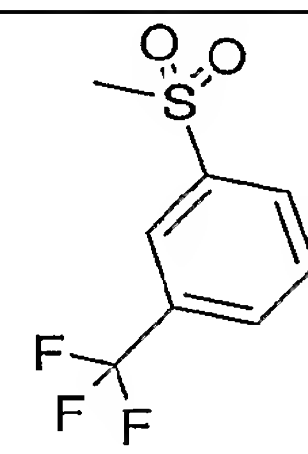
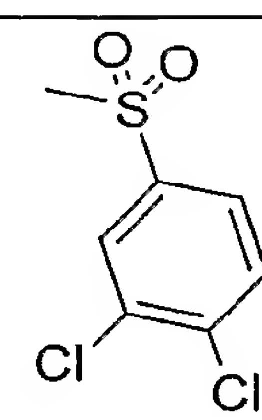
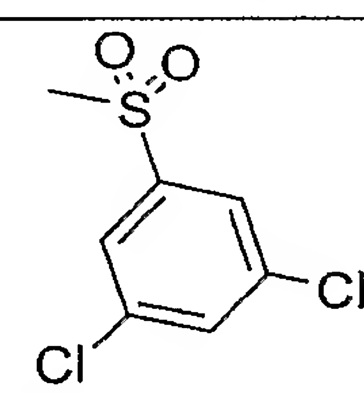
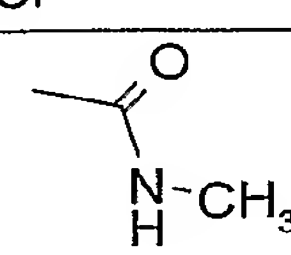
Example	Reagent	R	Measured Mass (M+H)
198	none		246.1712
199	Acetyl chloride		288.1845
200	Propionyl chloride		302.1989
201	Cyclopropanecarbonyl chloride		314.1982
202	Butyryl chloride		316.2153
203	Methoxyacetyl chloride		318.1920
204	Methyl chlorothiolformate		320.1528
205	Cyclopentylacetyl chloride		356.2448
206	*m*-Toluoyl chloride		364.2139
207	*p*-Toluoyl chloride		364.2139

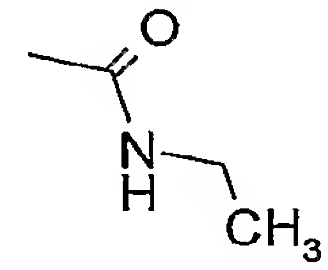
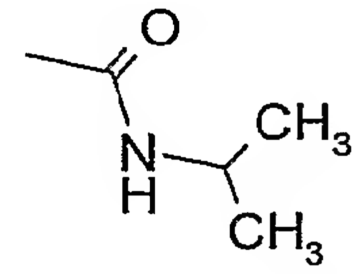
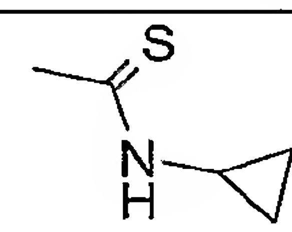
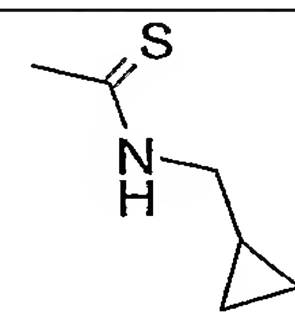
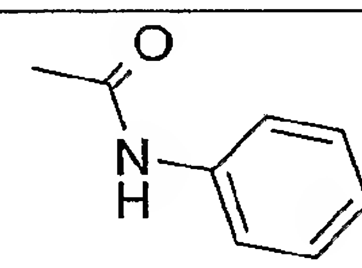
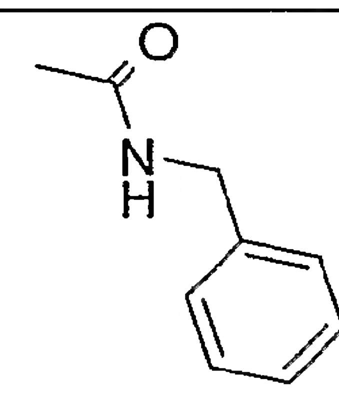
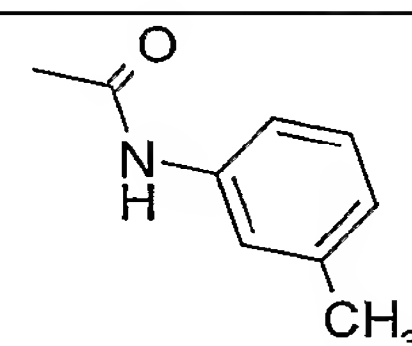
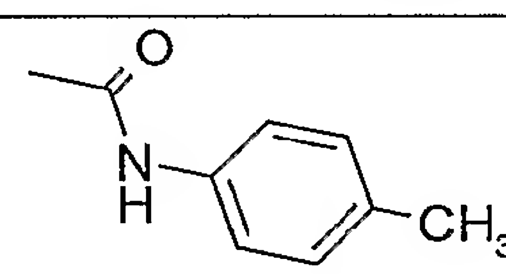
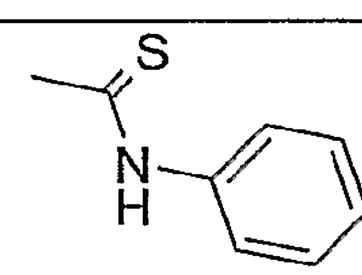
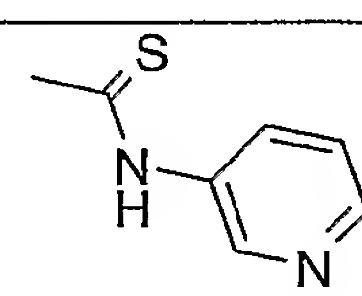
208	Phenylacetyl chloride		364.2135
209	3-Fluorobenzoyl chloride		368.1854
210	4-Fluorobenzoyl chloride		368.1859
211	3-Cyanobenzoyl chloride		375.1942
212	Hydrocinnamoyl chloride		378.2286
213	2-Methoxybenzoyl chloride		380.2076
214	3-Methoxybenzoyl chloride		380.2078
215	*p*-Anisoyl chloride		380.2050
216	2-Chlorobenzoyl chloride		384.1574

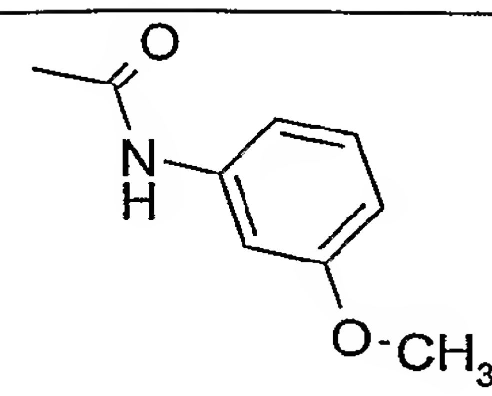
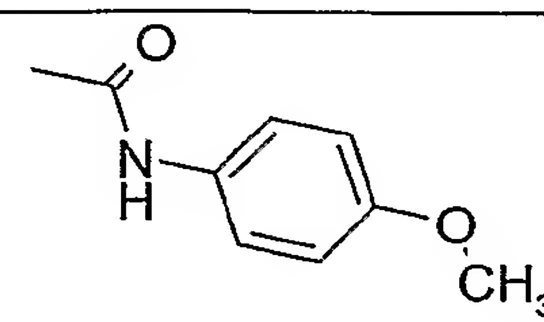
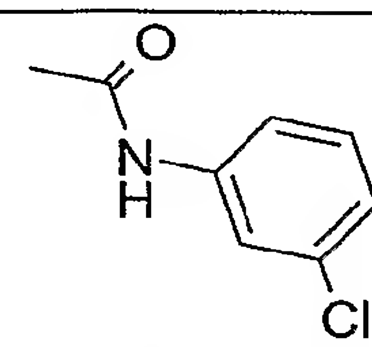
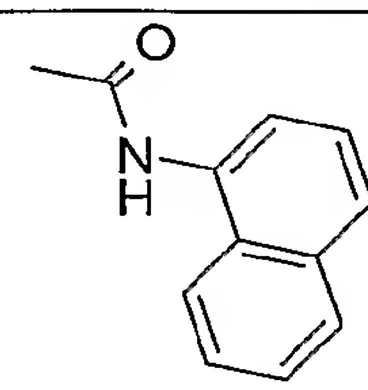
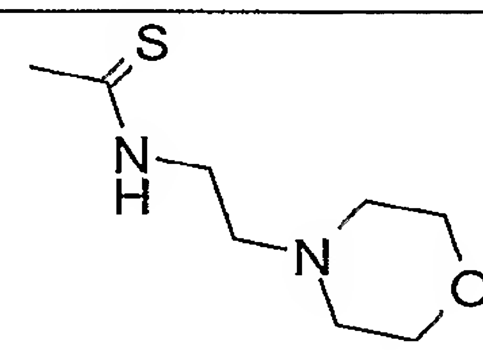
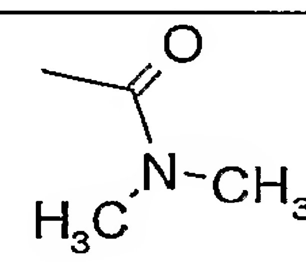
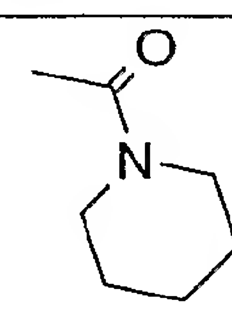
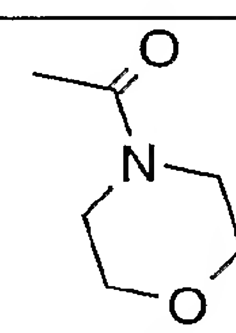
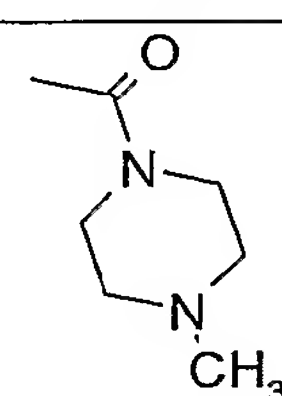
217	Isonicotinoyl chloride hydrochloride		351.1942
218	Nicotinoyl chloride hydrochloride		351.1934
219	Picolinoyl chloride hydrochloride		351.1912
220	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		390.2289
221	3,4-Dimethoxybenzoyl chloride		410.2179
222	3-(Trifluoromethyl)benzoyl chloride		418.1834
223	2,4-Dichlorobenzoyl chloride		418.1243
224	Methanesulfonyl chloride		324.1476
225	Ethanesulfonyl chloride		338.1645
226	1-Propanesulfonyl chloride		352.1780

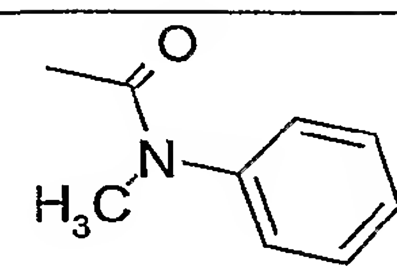
227	Dimethylsulfamoyl chloride		353.1751
228	1-Butanesulfonyl chloride		366.1972
229	Trifluoromethanesulfonyl chloride		378.1198
230	1-Methylimidazole-4-sulphonyl chloride		390.1730
231	2,2,2-Trifluoroethanesulfonyl chloride		392.1344
232	3-Methylbenzenesulfonyl chloride		400.1787
233	*alpha*-Toluenesulfonyl chloride		400.1801
234	2-Fluorobenzenesulfonyl chloride		404.1536
235	3-Fluorobenzenesulfonyl chloride		404.1560

236	4-Fluorobenzenesulfonyl chloride		404.1543
237	3-Cyanobenzenesulfonyl chloride		411.1613
238	4-Cyanobenzenesulfonyl chloride		411.1631
239	*beta*-Styrenesulfonyl chloride		412.1797
240	3-Methoxybenzenesulfonyl chloride		416.1752
241	4-Methoxybenzenesulfonyl chloride		416.1774
242	2-Chlorobenzenesulfonyl chloride		420.1244

243	3-Chlorobenzenesulfonyl chloride		420.1227
244	2-Naphthalenesulfonyl chloride		436.1782
245	*N*-Acetylsulfanilyl chloride		443.1829
246	3,4-Dimethoxybenzenesulfonyl chloride		446.1832
247	3-(Trifluoromethyl)benzenesulfonyl chloride		454.1510
248	3,4-Dichlorobenzenesulfonyl chloride		454.0905
249	3,5-Dichlorobenzenesulfonyl chloride		454.0891
250	Methyl isocyanate		303.1942

251	Ethyl isocyanate		317.2078
252	Isopropyl isocyanate		331.2234
253	Cyclopropyl isothiocyanate		345.1847
254	Cyclopropylmethyl isothiocyanate		359.2050
255	Phenyl isocyanate		365.2102
256	Benzyl isocyanate		379.2238
257	*m*-Tolyl isocyanate		379.2245
258	*p*-Tolyl isocyanate		379.2234
259	Phenyl isothiocyanate		381.1844
260	3-Pyridyl isothiocyanate		382.1807

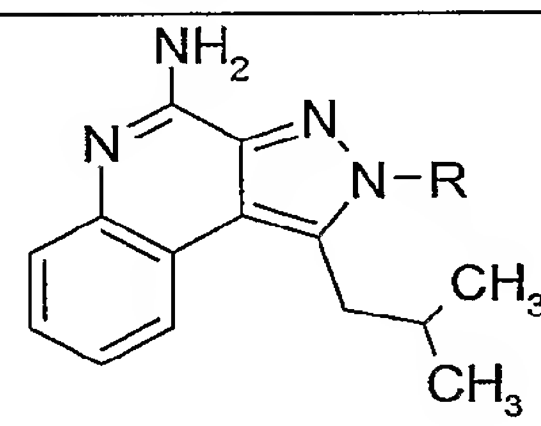
261	3-Methoxyphenyl isocyanate		395.2202
262	4-Methoxyphenyl isocyanate		395.2234
263	3-Chlorophenyl isocyanate		399.1696
264	1-Naphthyl isocyanate		415.2243
265	2-Morpholinoethyl isothiocyanate		418.2388
266	*N*,*N*-Dimethylcarbamoyl chloride		317.2071
267	1-Piperidinecarbonyl chloride		357.2418
268	4-Morpholinylcarbonyl chloride		359.2209
269	4-Methyl-1-piperazinecarbonyl chloride		372.2527

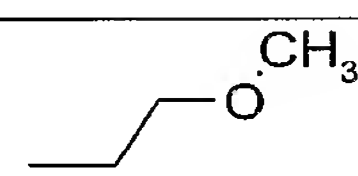
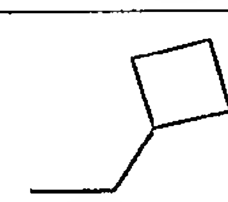
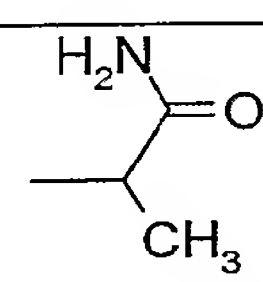
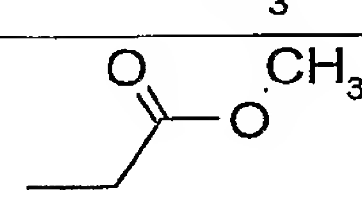
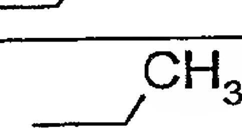
270	*N*-Methyl-*N*-phenylcarbamoyl chloride		379.2267

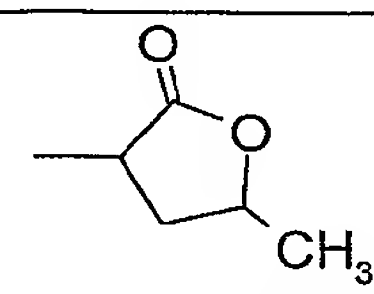
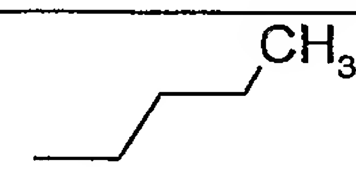
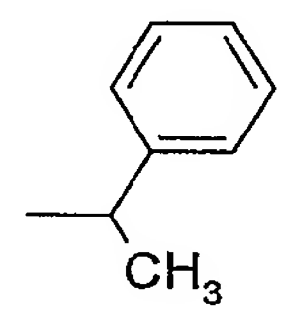
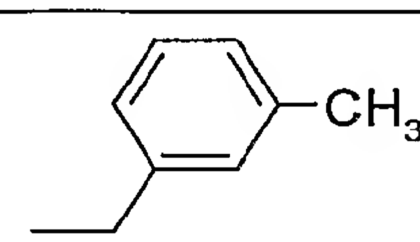
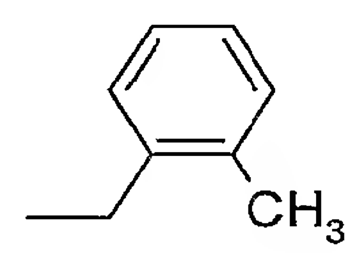
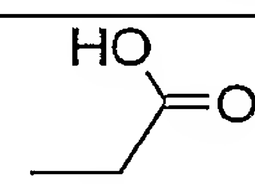
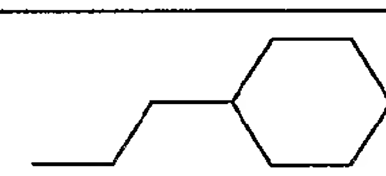
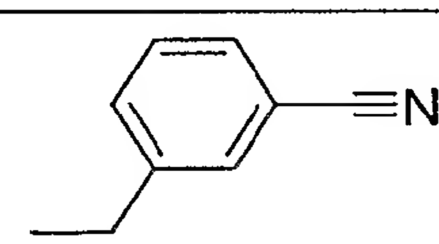
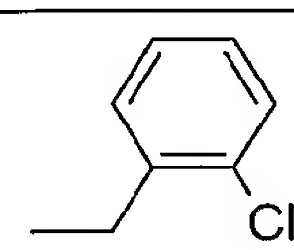
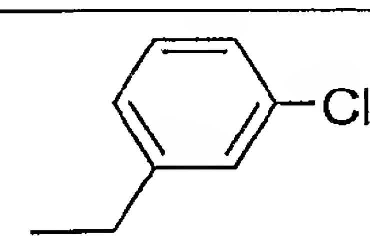
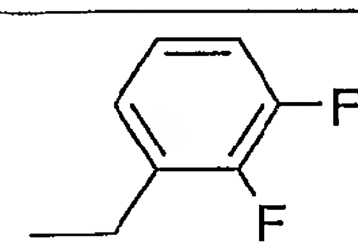
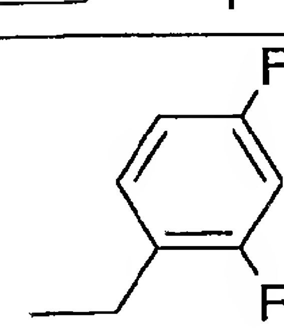
Examples 271-306

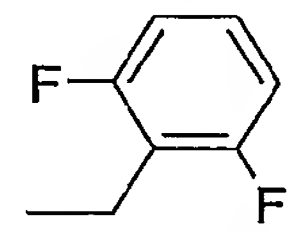
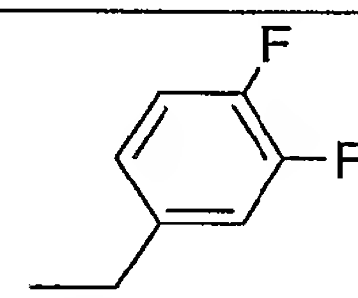
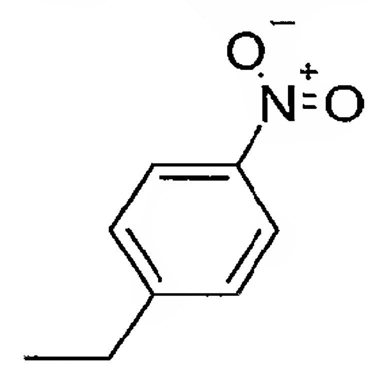
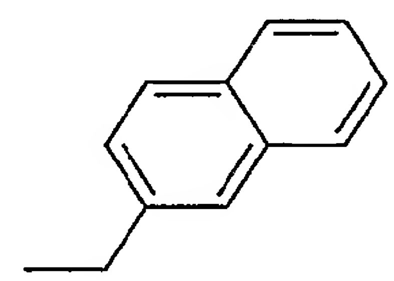
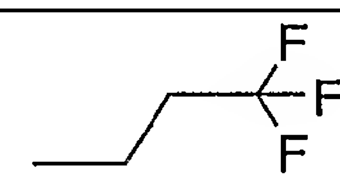
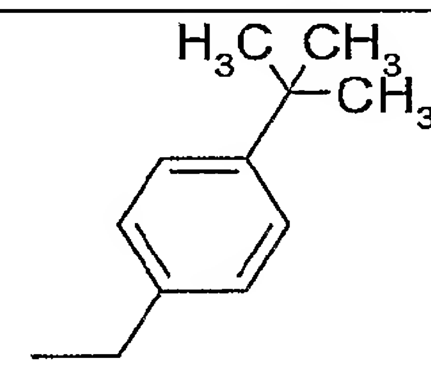
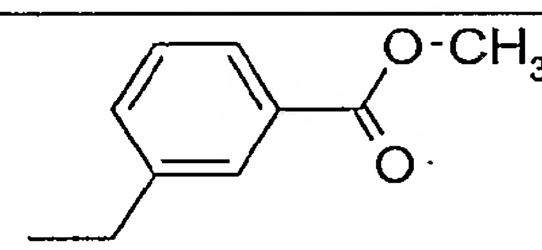
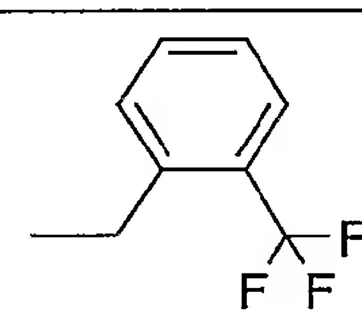
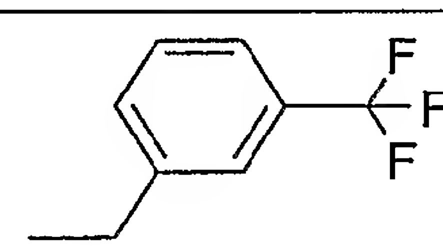
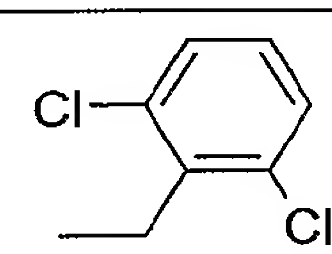
A reagent (0.14 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 9, 32 mg, 0.13 mmol) and potassium carbonate (approximately 55 mg, 0.40 mmol) in DMF (1 mL). A stirbar was added to each test tube. The test tubes were capped and stirred overnight (approximately 18 horus) at ambient temperature. The reaction mixtures were filtered and the solvent was removed from the filtrates by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

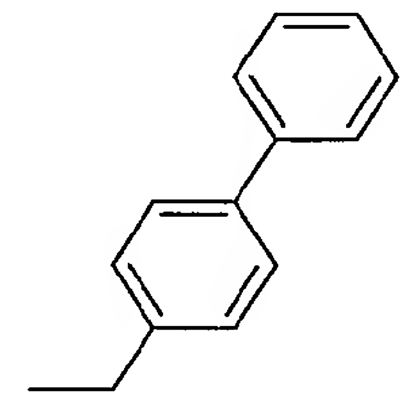
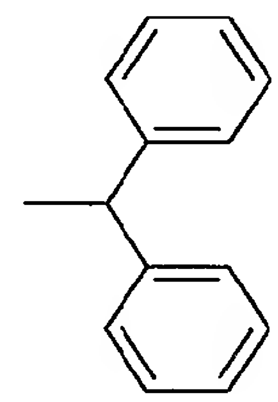
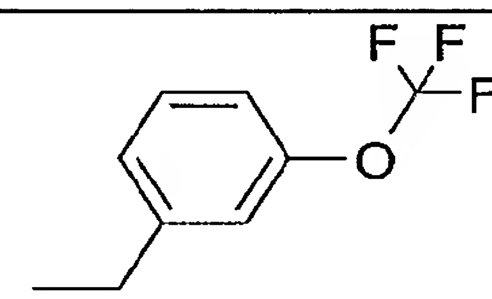
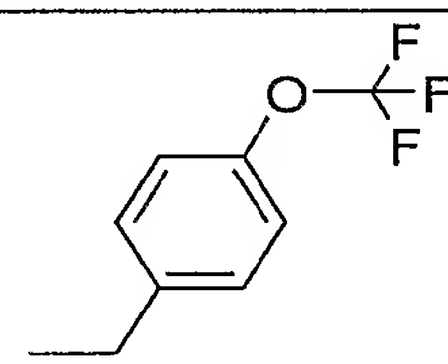
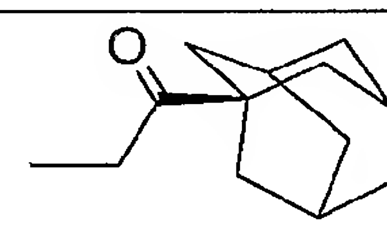
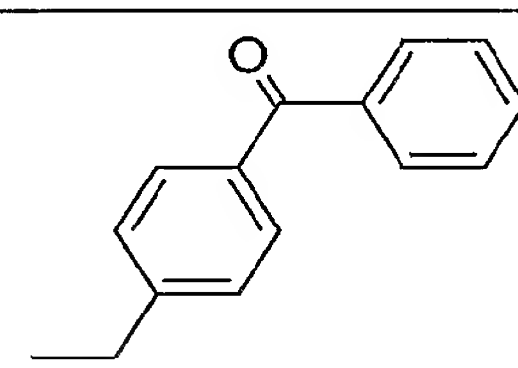
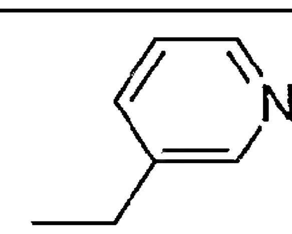
Examples 271-306



Example	Reagent	R	Measured Mass (M+H)
271	2-Bromoethyl methyl ether		299.1857
272	Iodomethane	$-CH_3$	255.1599
273	Cyclobutylmethyl bromide		309.2067
274	2-Bromopropanamide		312.1841
275	Methyl bromoacetate		313.1661
276	Iodoethane		269.1758

277	2-Iodoethanol		285.1724
278	2-Bromo-4-hydroxvaleric acid *gamma*-lactone		339.1794
279	1-Iodobutane		297.2073
280	(1-Bromoethyl)benzene		345.2084
281	*alpha*-Bromo-*m*-xylene		345.2065
282	*alpha*-Bromo-*o*-xylene		345.2049
283	Iodoacetic acid		299.1503
284	2-Cyclohexylethyl bromide		351.2532
285	*alpha*-Bromo-*m*-tolunitrile		356.1871
286	2-Chlorobenzyl bromide		365.1530
287	3- Chlorobenzyl bromide		365.1534
288	2,3- Difluorobenzyl bromide		367.1741
289	2,4-Difluorobenzyl bromide		367.1734

290	2,6- Difluorobenzyl bromide		367.1718
291	3,4- Difluorobenzyl bromide		367.1704
292	4- Nitrobenzyl bromide		376.1784
293	2-(Bromomethyl)naphthalene		381.2071
294	1-Iodo-3,3,3-trifluoropropane		337.1628
295	4-(*tert*-Butyl)benzyl bromide		387.2564
296	Methyl 3-(bromomethyl)benzoate		389.1986
297	2-(Trifluoromethyl)benzyl bromide		399.1796
298	3-(Trifluoromethyl)benzyl bromide		399.1790
299	2,6-Dichlorobenzyl bromide		399.1157

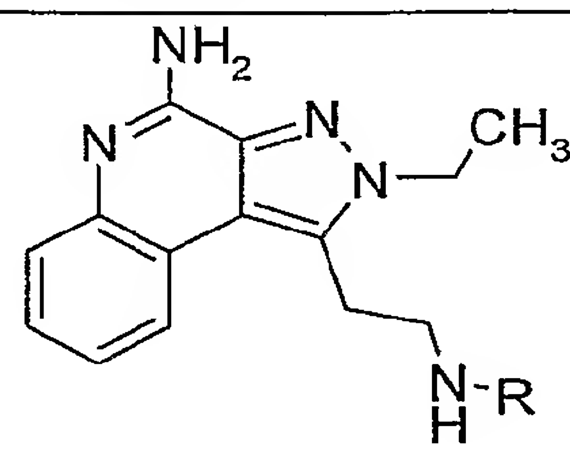
300	4-Bromomethylbiphenyl		407.2252
301	Bromodiphenylmethane		407.2248
302	3-(Trifluoromethoxy)benzyl bromide		415.1747
303	4-(Trifluoromethoxy)benzyl bromide		415.1759
304	1-Adamantyl bromomethyl ketone		417.2643
305	4-(Bromomethyl)benzophenone		435.2195
306	2-(Bromoacetyl)pyridine hydrobromide		332.1870

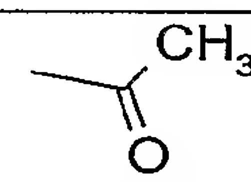
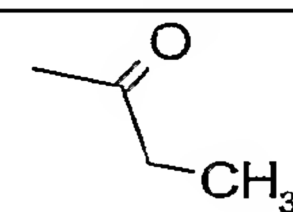
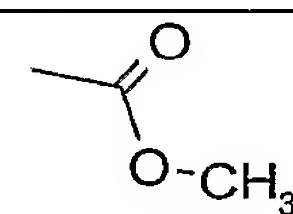
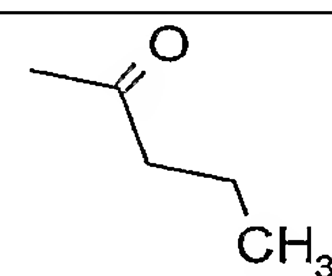
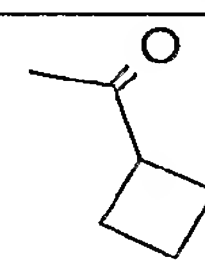
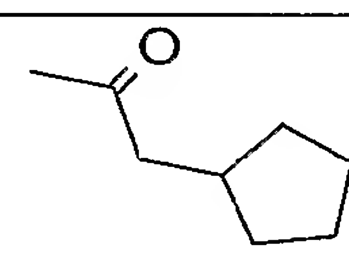
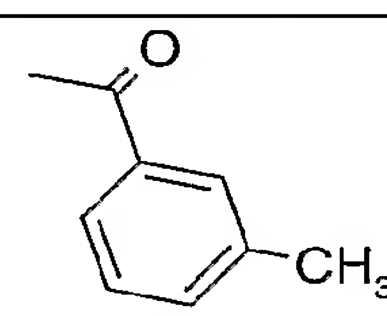
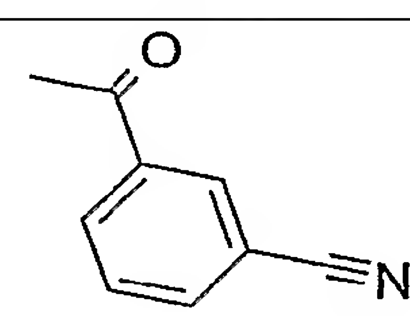
Examples 307-348

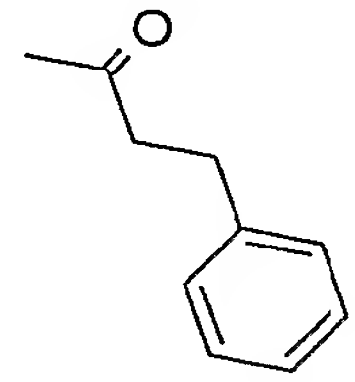
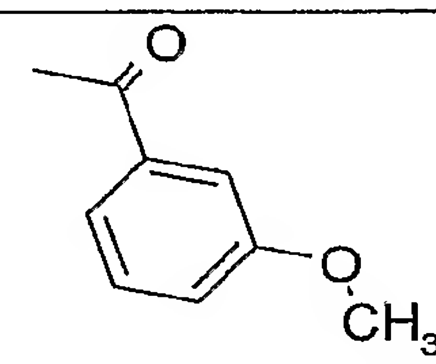
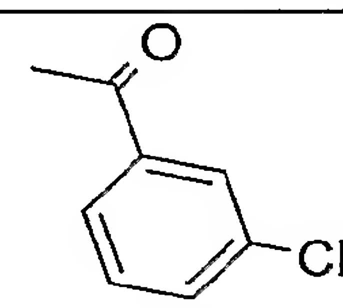
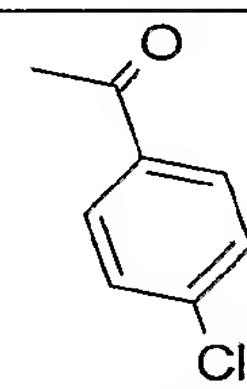
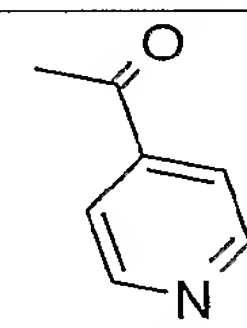
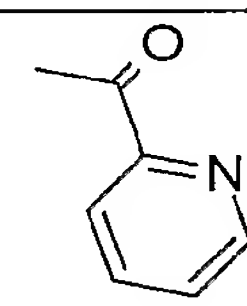
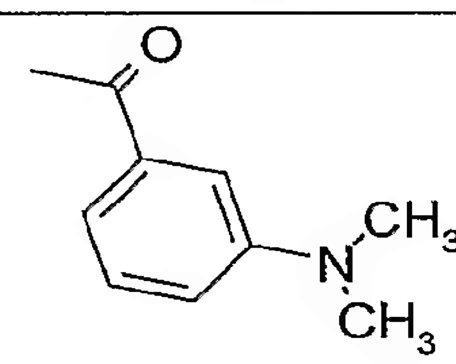
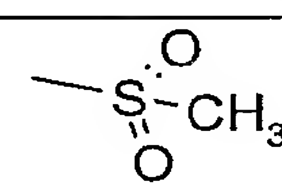
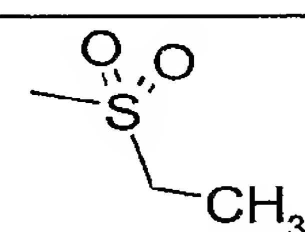
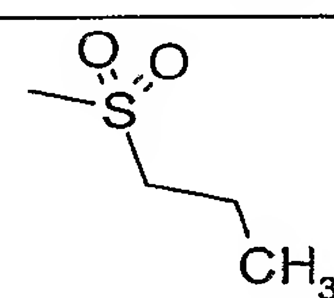
A solution of 1-(2-aminoethyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride (prepared as described in Example 23, 33 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.070 mL, 0.40 mmol) in chloroform (1 mL) was treated with a reagent (0.11 mmol, 1.1 equivalents) from the table below using the procedure described in Examples 23-33. The test tubes were capped and shaken overnight at ambient temperature, then were worked up and purified as described in Examples 23-33. The table

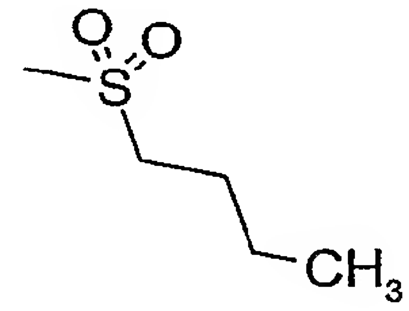
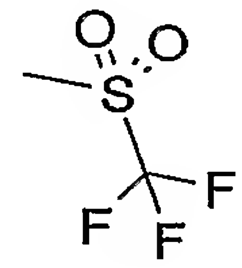
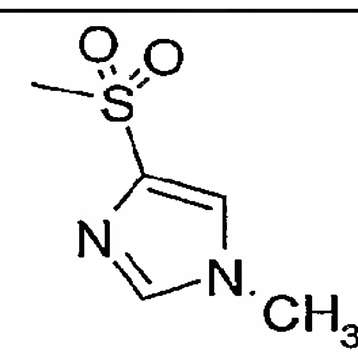
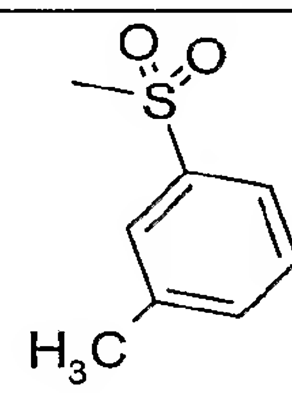
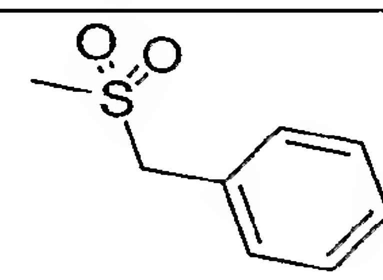
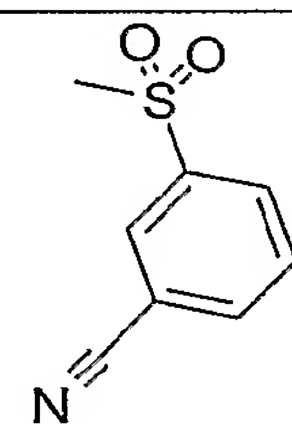
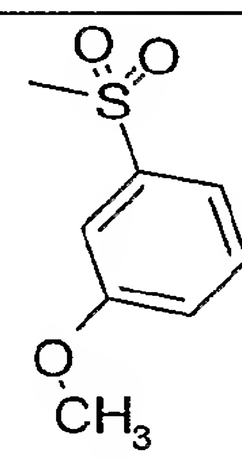
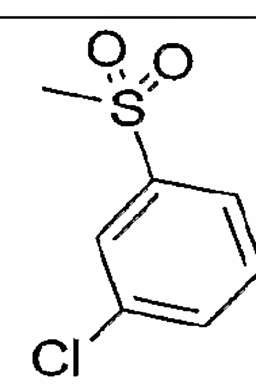
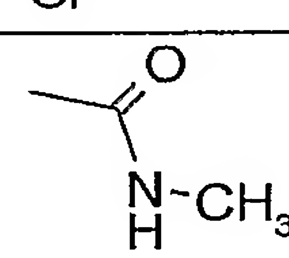
below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

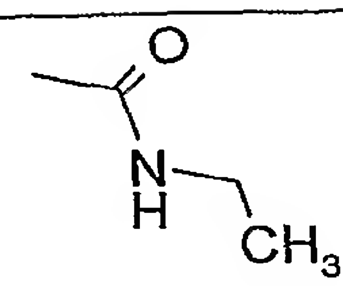
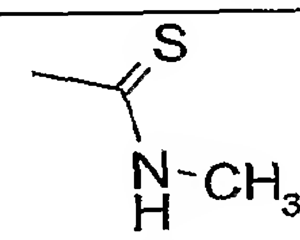
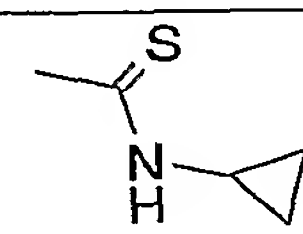
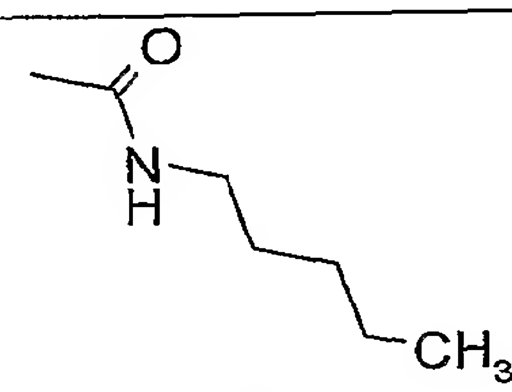
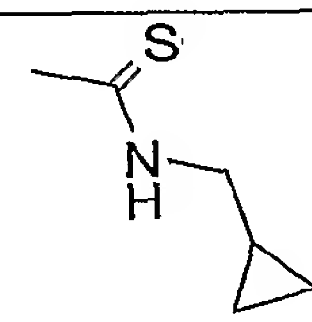
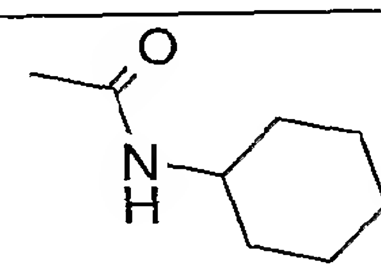
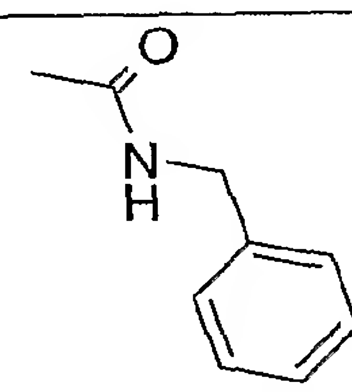
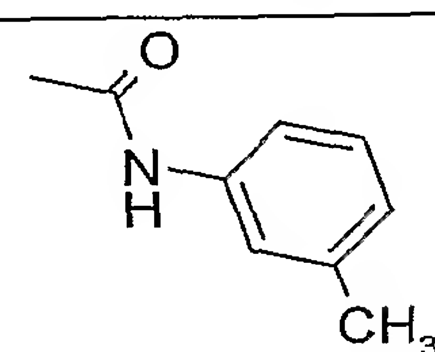
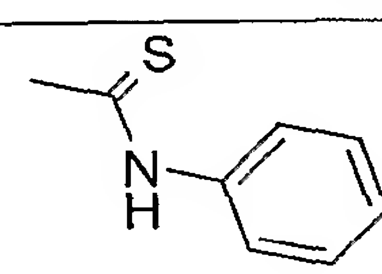
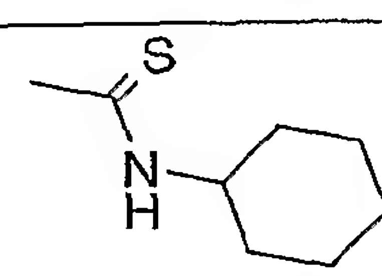
Examples 307-348

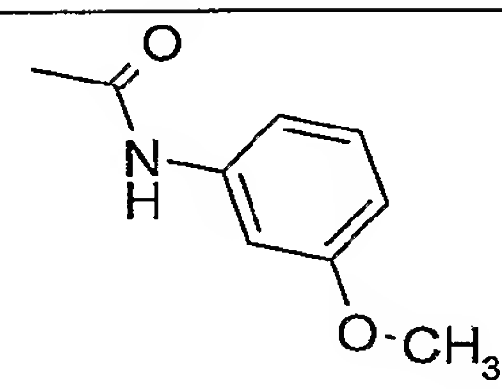
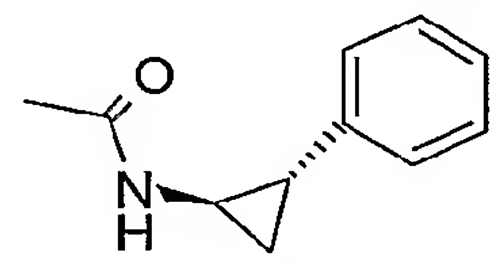
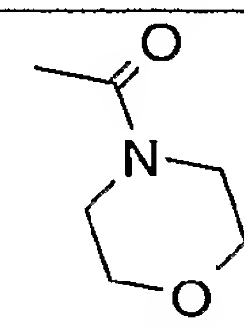
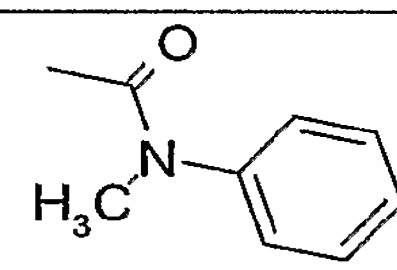


Example	Reagent	R	Measured Mass (M+H)
307	Acetyl chloride		298.1668
308	Propionyl chloride		312.1841
309	Methyl chloroformate		314.1601
310	Butryl chloride		326.1995
311	Cyclobutanecarbonyl chloride		338.1966
312	Cyclopentylacetyl chloride		366.2291
313	*m*-Toluoyl chloride		374.2002
314	3-Cyanobenzoyl chloride		385.1764

315	Hydrocinnamoyl chloride		388.2147
316	3-Methoxybenzoyl chloride		390.1935
317	3-Chlorobenzoyl chloride		394.1436
318	4-Chlorobenzoyl chloride		394.1441
319	Isonicotinoyl chloride hydrochloride		361.1778
320	Picolinoyl chloride hydrochloride		361.1762
321	3-Dimethylaminobenzoyl chloride		403.2254
322	Methanesulfonyl chloride		334.1329
323	Ethanesulfonyl chloride		348.1497
324	1-Propanesulfonyl chloride		362.1642

325	1-Butanesulfonyl chloride		376.1806
326	Trifluoromethanesulfonyl chloride		388.1048
327	1-Methylimidazole-4-sulfonyl chloride		400.1549
328	3-Methylbenzenesulfonyl chloride		410.1651
329	*alpha*-Toluenesulfonyl chloride		410.1644
330	3-Cyanobenzenesulfonyl chloride		421.1447
331	3-Methoxylbenzenesulfonyl chloride		426.1591
332	3-Chlorobenzenesulfonyl chloride		430.1097
333	Methyl isocyanate		313.1771

334	Ethyl isocyanate		327.1921
335	Methyl isothiocyanate		329.1542
336	Cyclopropyl isothiocyanate		355.1706
337	Pentyl isocyanate		369.2397
338	Cyclopropylmethyl isothiocyanate		369.1848
339	Cyclohexyl isocyanate		381.2404
340	Benzyl isocyanate		389.2104
341	*m*-Tolyl isocyanate		389.2086
342	Phenyl isothiocyanate		391.1704
343	Cyclohexyl isothiocyanate		397.2166

345	3-Methoxyphenyl isocyanate		405.2052
346	*trans*-2-Phenylcyclopropyl isocyanate		415.2250
347	4-Morpholinylcarbonyl chloride		369.2028
348	*N*-Methyl-*N*-phenylcarbamoyl chloride		389.2051

Examples 349-453

Part A

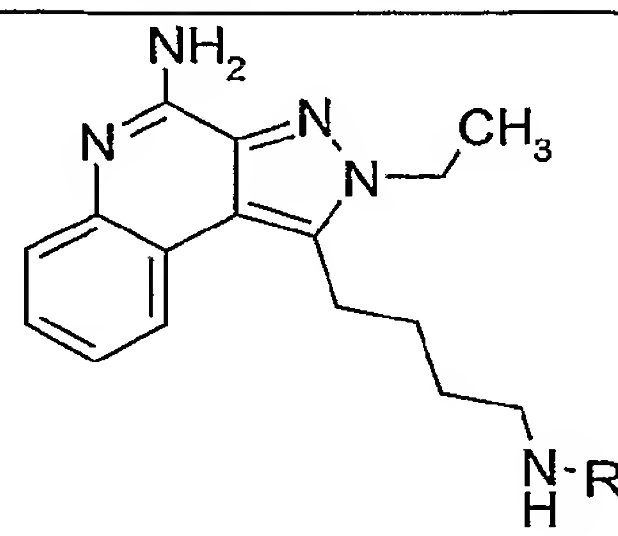
2-[4-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]isoindole-1,3-dione (prepared as described in Example 22, 7.10 g, 17.2 mmol), hydrazine hydrate (4.20 mL, 85.9 mmol), and ethanol (213 mL) were combined and heated at reflux for 30 minutes. The solution was allowed to cool to ambient temperature, then was cooled to 0 °C. A white solid precipitated from the solution and was isolated by filtration and washed with ethanol. The crude product was purified by chromatography on a HORIZON HPFC system (silica, gradient elution with 10%-75% CMA in chloroform). The appropriate fractions were combined and concentrated under reduced pressure to afford 4.25 g of 1-(4-aminobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine.

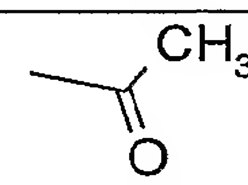
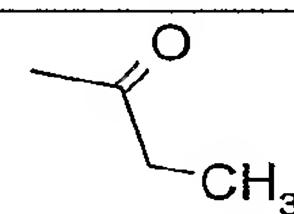
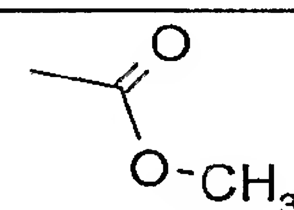
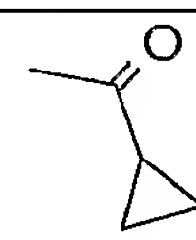
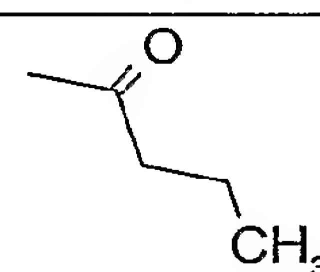
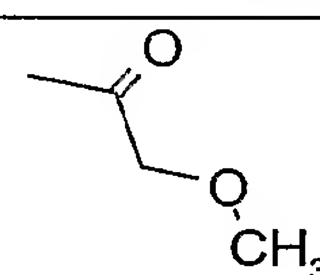
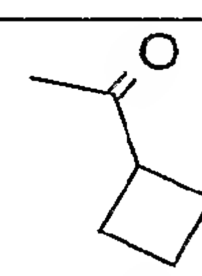
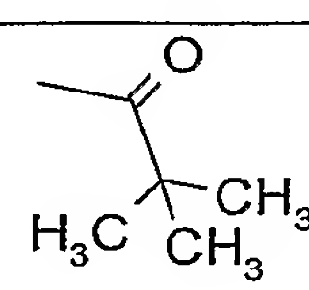
Part B

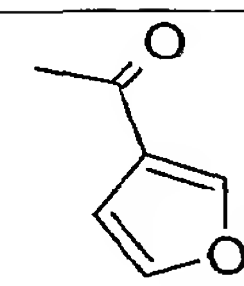
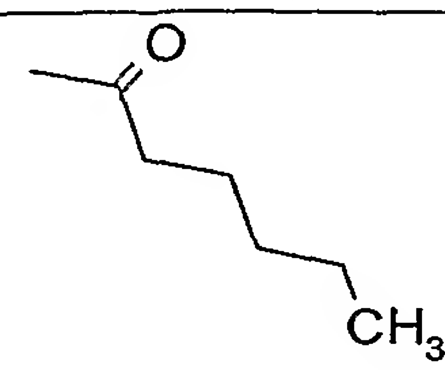
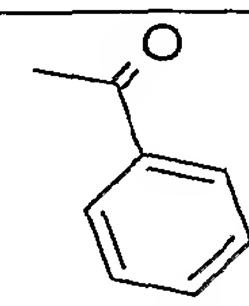
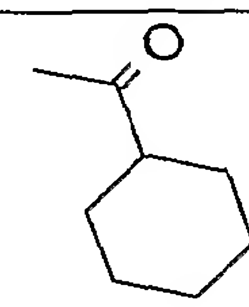
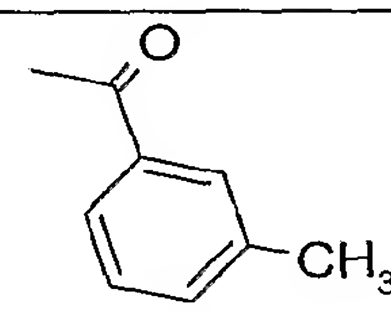
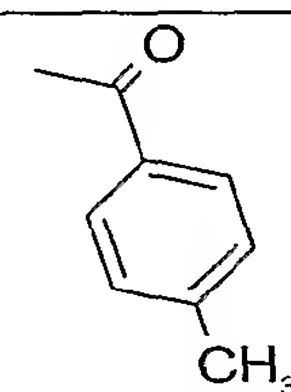
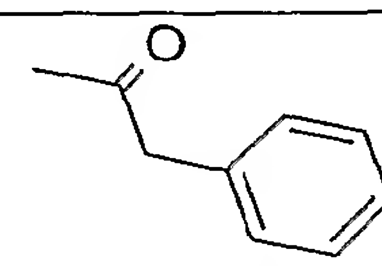
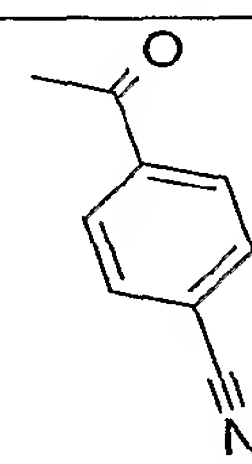
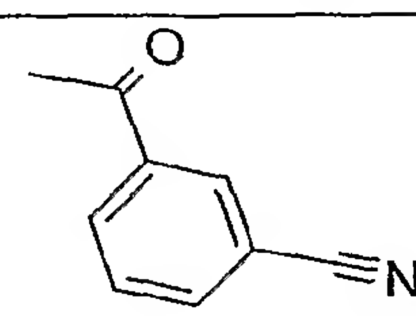
A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(4-aminobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (28 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.026 mL, 0.15 mmol) in chloroform (1 mL). The test tubes were capped and the test tubes were shaken overnight at room temperature and then two drops of water were added to each test tube. The solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85.

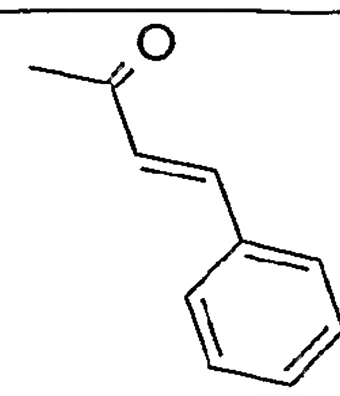
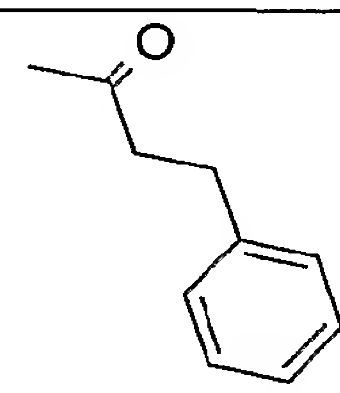
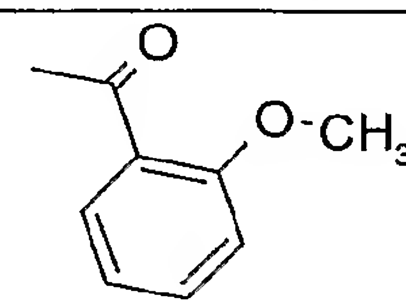
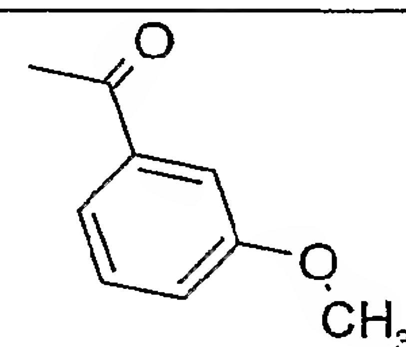
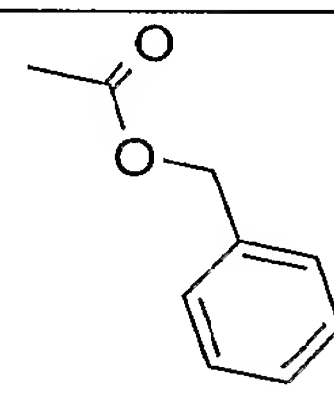
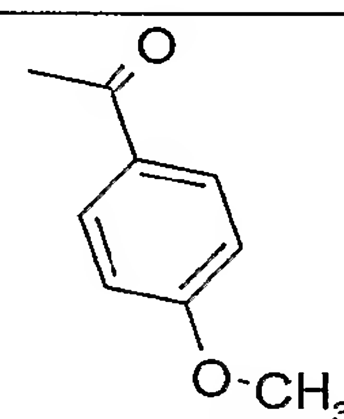
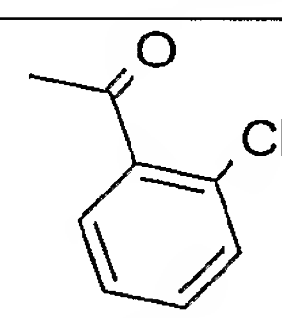
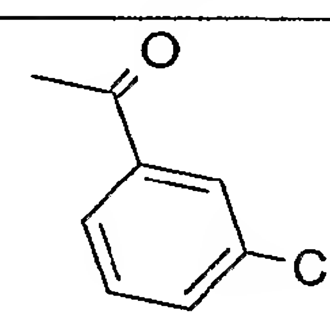
The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

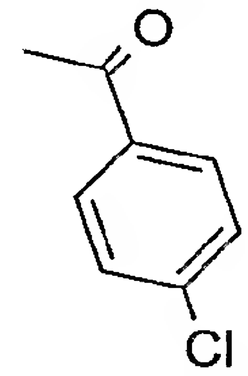
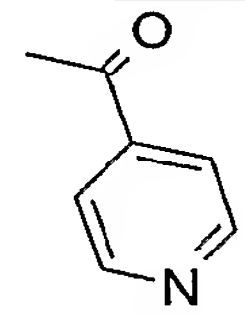
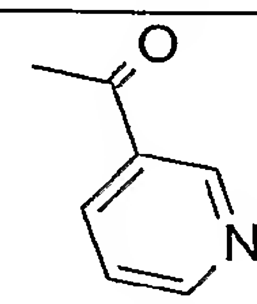
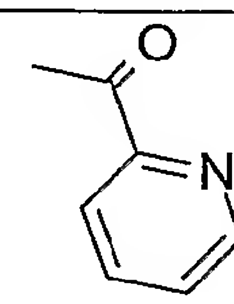
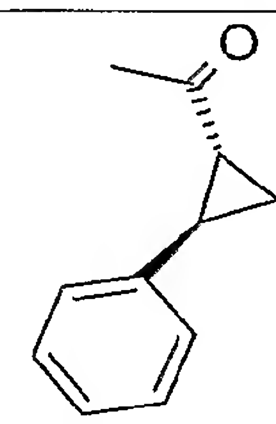
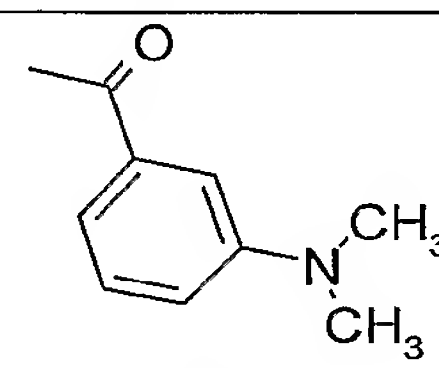
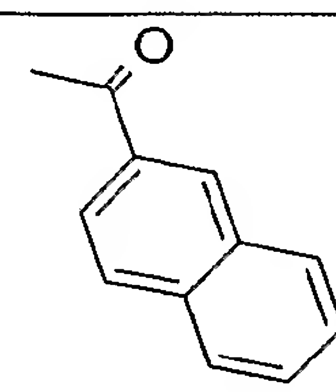
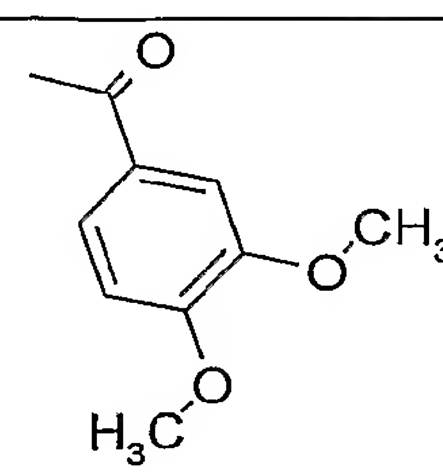
Examples 349-453

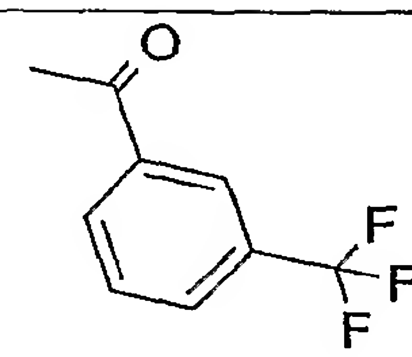
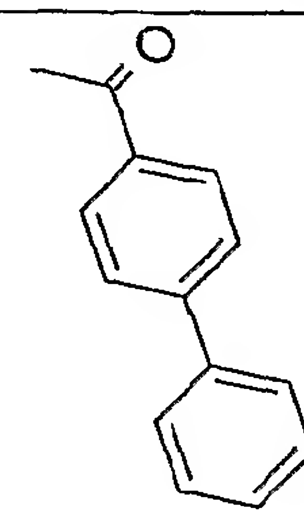
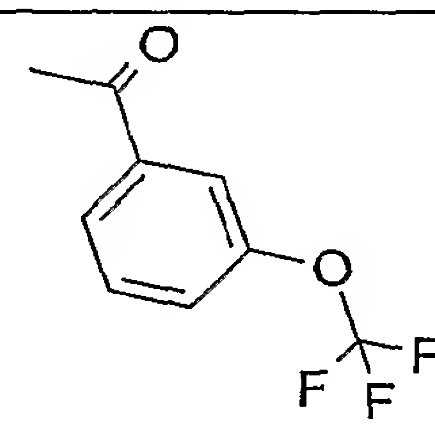
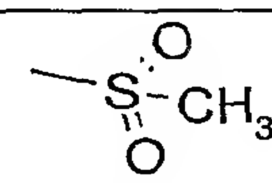
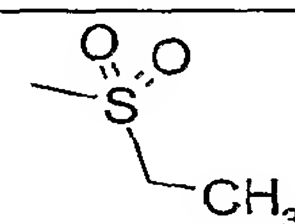
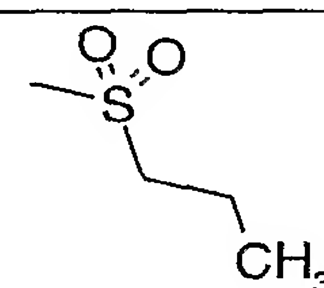
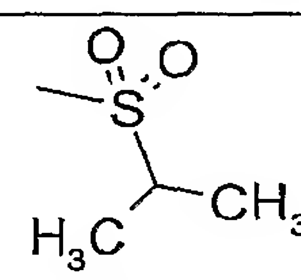
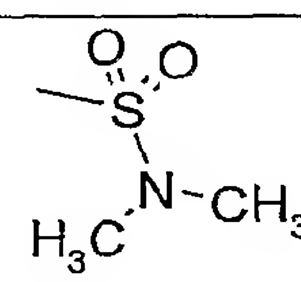
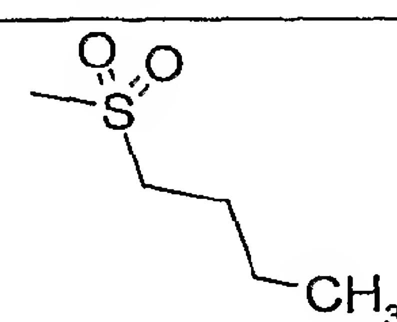
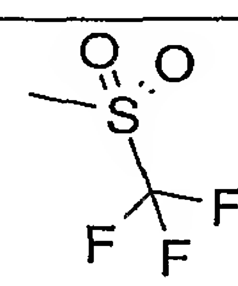


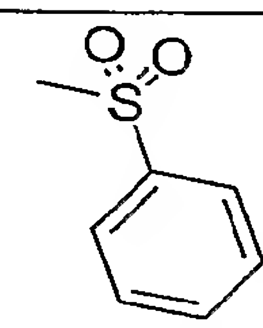
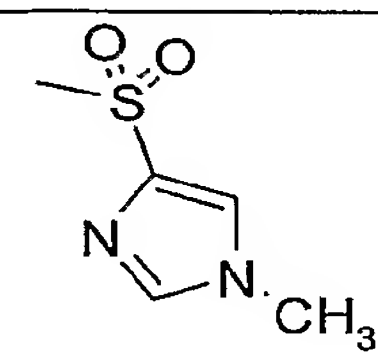
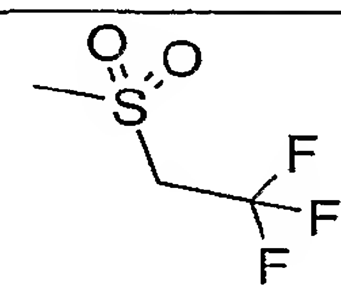
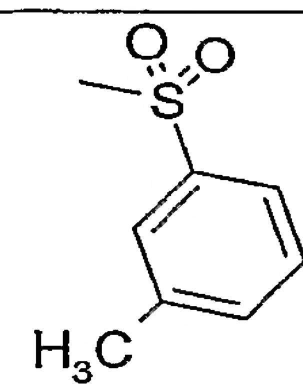
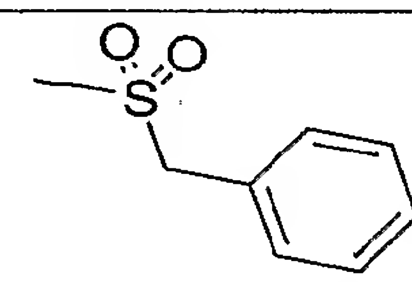
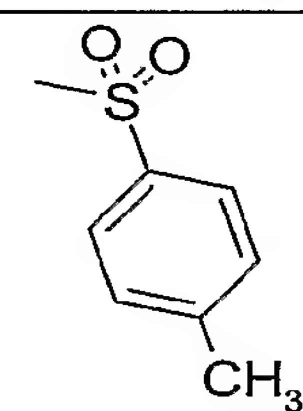
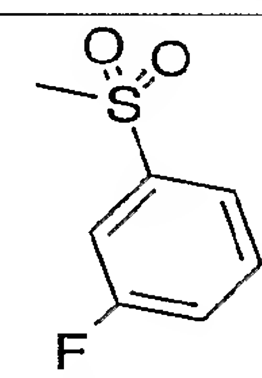
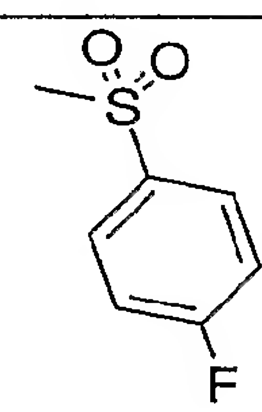
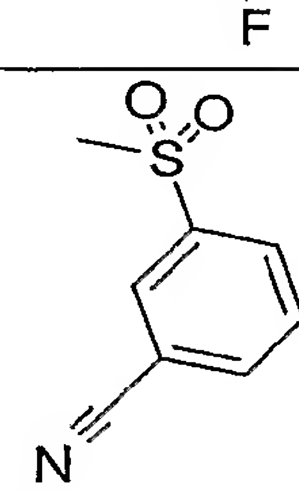
Example	Reagent	R	Measured Mass (M+H)
349	none		284.1877
350	Acetyl chloride		326.1978
351	Propionyl chloride		340.2140
352	Methyl chloroformate		342.1937
353	Cyclopropanecarbonyl chloride		352.2149
354	Butyryl chloride		354.2276
355	Methoxyacetyl chloride		356.2112
356	Cyclobutanecarbonyl chloride		366.2305
357	Pivaloyl chloride		368.2444

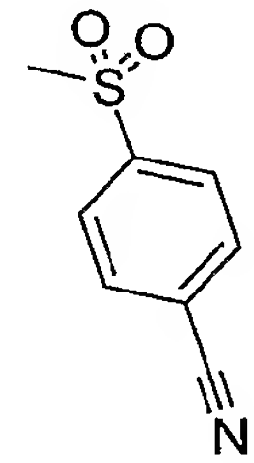
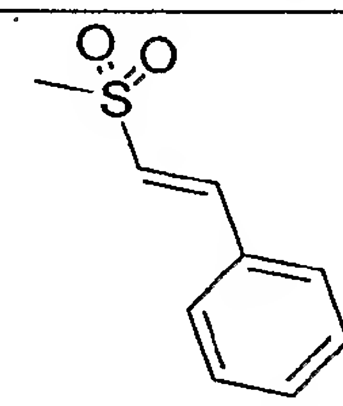
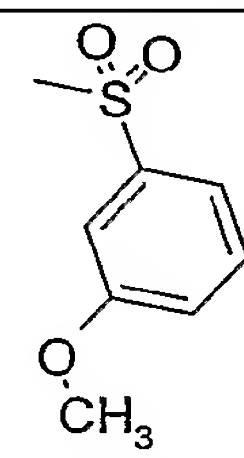
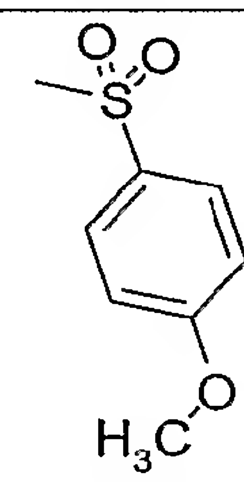
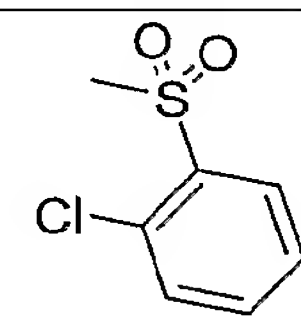
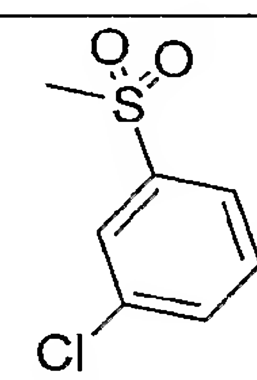
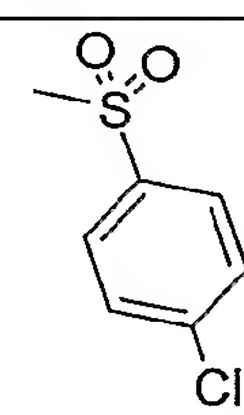
358	3-Furoyl chloride		378.1927
359	Hexanoyl chloride		382.2627
360	Benzoyl chloride		388.2150
361	Cyclohexanecarbonyl chloride		394.2607
362	*m*-Toluoyl chloride		402.2298
363	*p*-Toluoyl chloride		402.2291
364	Phenylacetyl chloride		402.2286
365	4-Cyanobenzoyl chloride		413.2110
366	3-Cyanobenzoyl chloride		413.2065

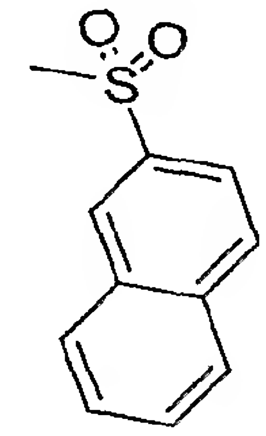
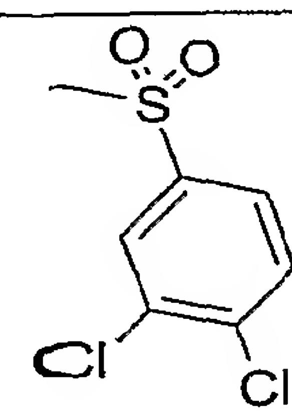
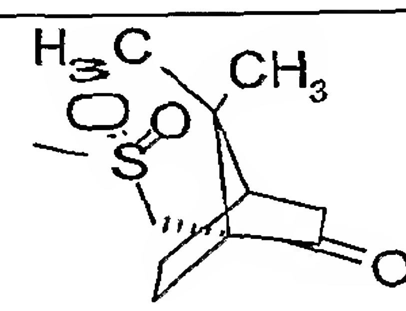
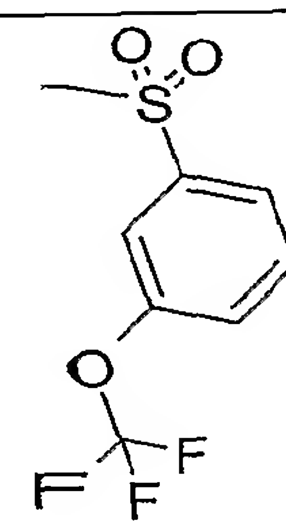
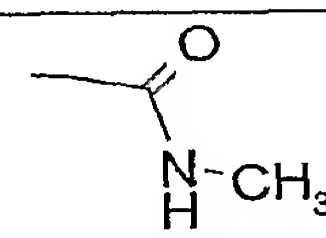
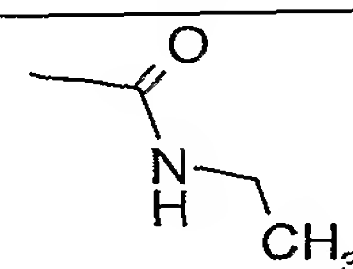
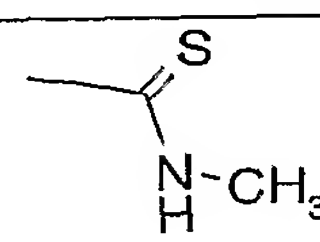
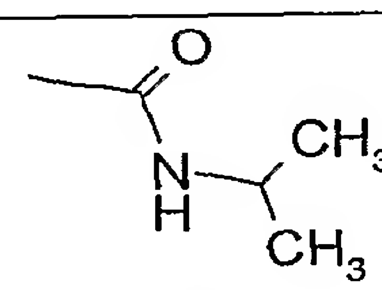
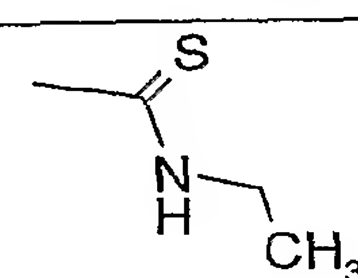
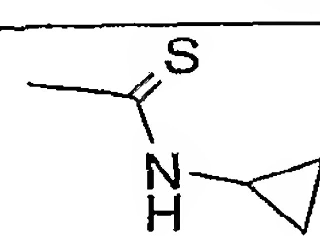
367	Cinnamoyl chloride		414.2303
368	Hydrocinnamoyl chloride		416.2462
369	2-Methoxybenzoyl chloride		418.2260
370	3-Methoxybenzoyl chloride		418.2227
371	Benzyl chloroformate		418.2251
372	*p*-Anisoyl chloride		418.2253
373	2-Chlorobenzoyl chloride		422.1730
374	3-Chlorobenzoyl chloride		422.1746

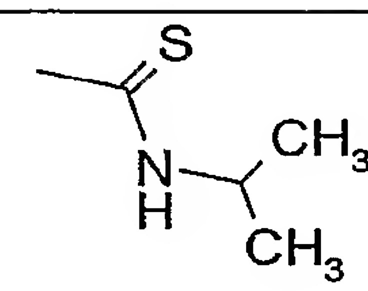
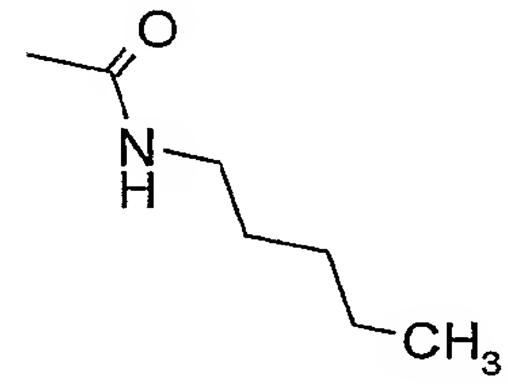
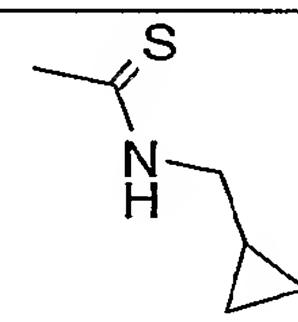
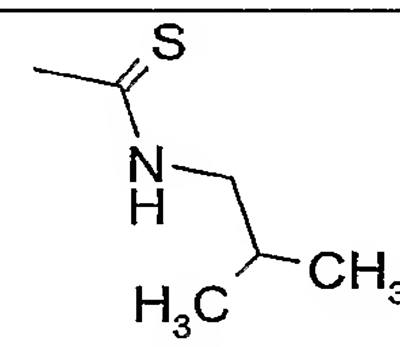
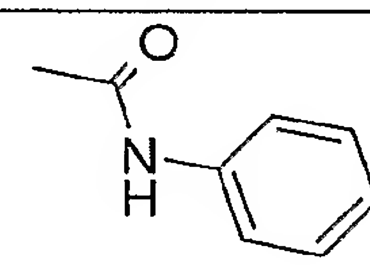
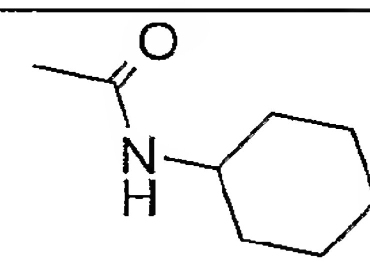
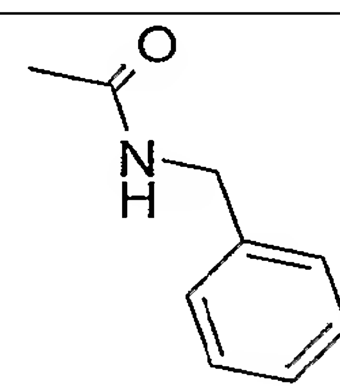
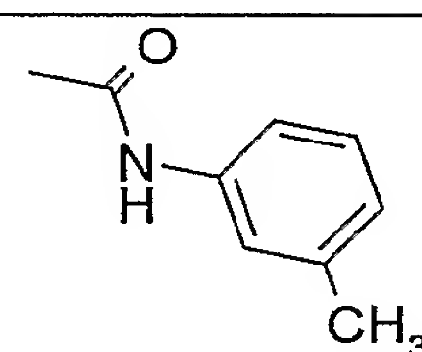
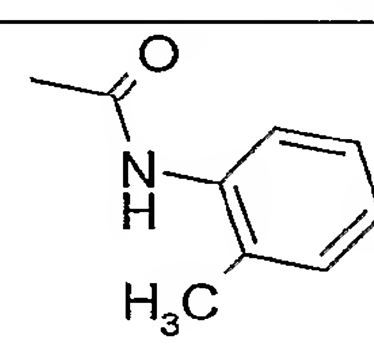
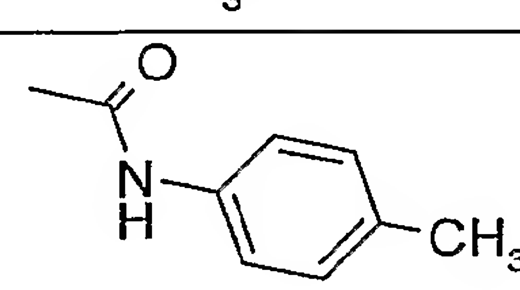
375	4-Chlorobenzoyl chloride		422.1752
376	Isonicotinoyl chloride hydrochloride		389.2069
377	Nicotinoyl chloride hydrochloride		389.2081
378	Picolinoyl chloride hydrochloride		389.2097
379	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		428.2440
380	3-Dimethylaminobenzoyl chloride		431.2560
381	2-Naphthoyl chloride		438.2295
382	3,4-Dimethoxybenzoyl chloride		448.2343

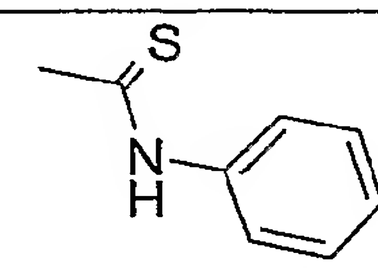
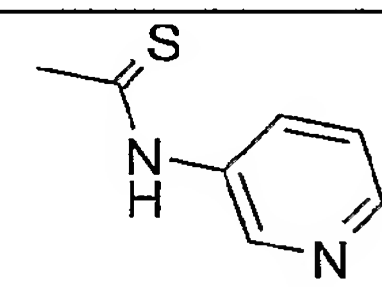
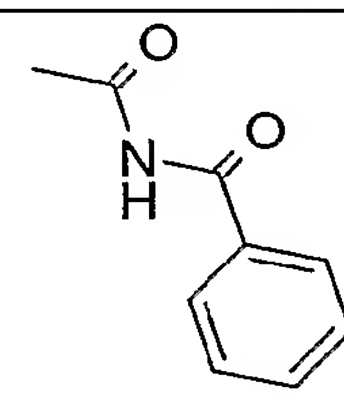
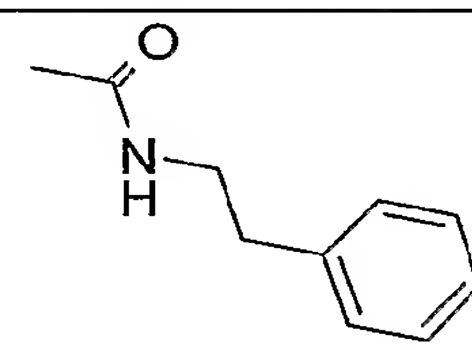
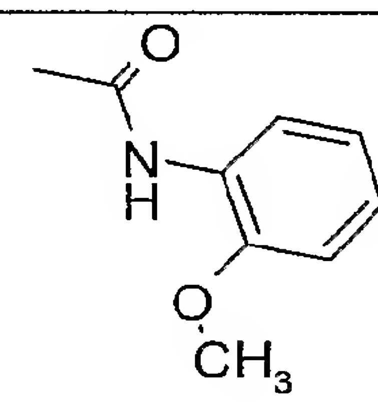
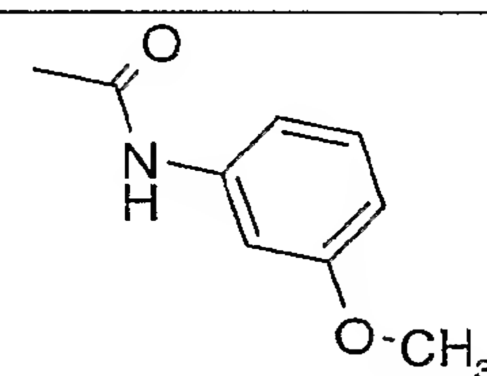
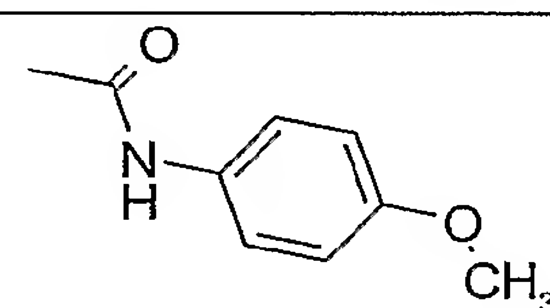
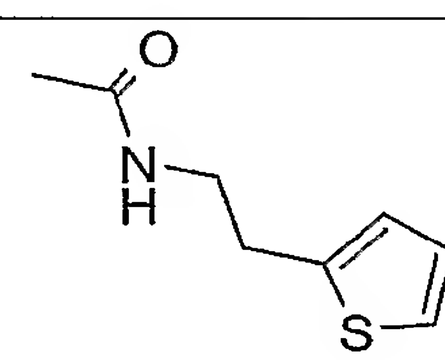
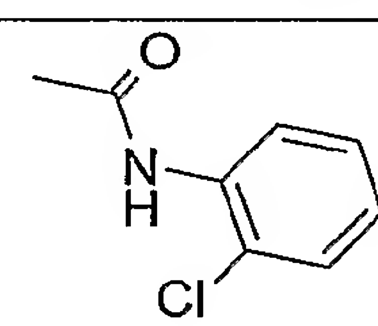
383	3-(Trifluoromethyl)benzoyl chloride		456.2019
384	4-Biphenylcarbonyl chloride		464.2492
385	3-(Trifluoromethoxy)benzoyl chloride		472.1953
386	Methanesulfonyl chloride		362.1651
387	Ethanesulfonyl chloride		376.1832
388	1-Propanesulfonyl chloride		390.1955
389	Isopropylsulfonyl chloride		390.1954
390	Dimethylsulfamoyl chloride		391.1898
391	1-Butanesulfonyl chloride		404.2154
392	Trifluoromethanesulfonyl chloride		416.1362

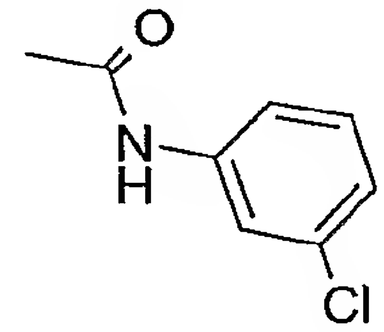
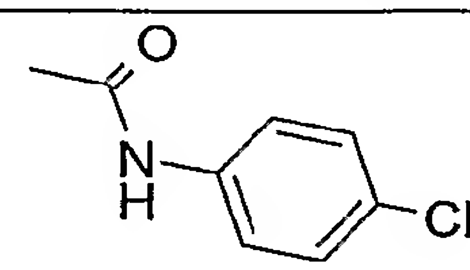
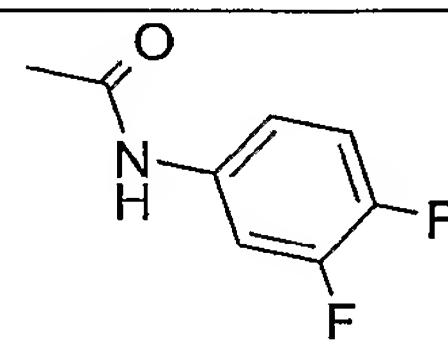
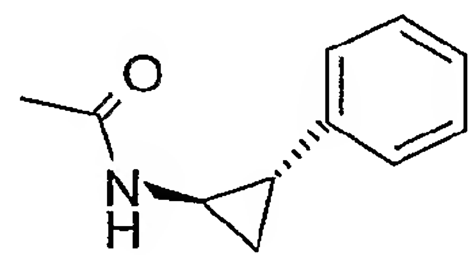
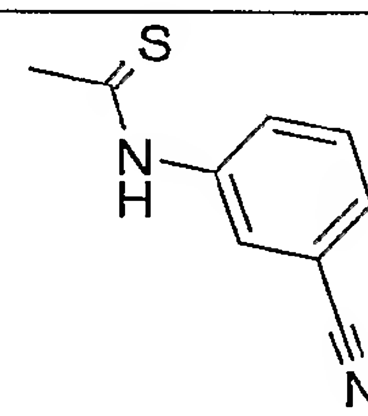
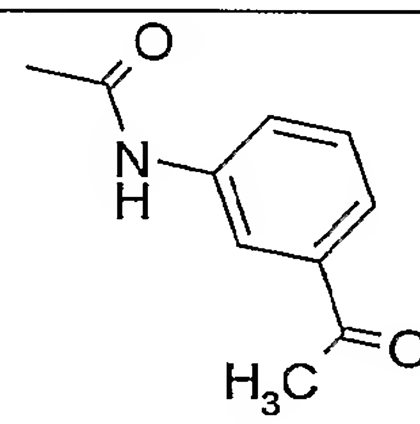
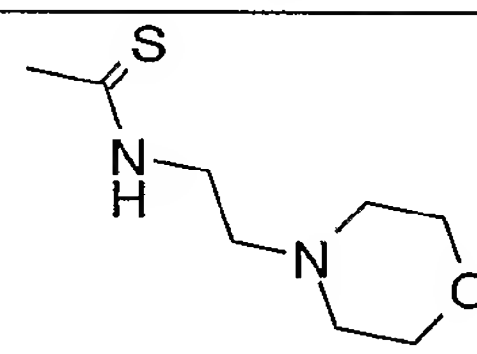
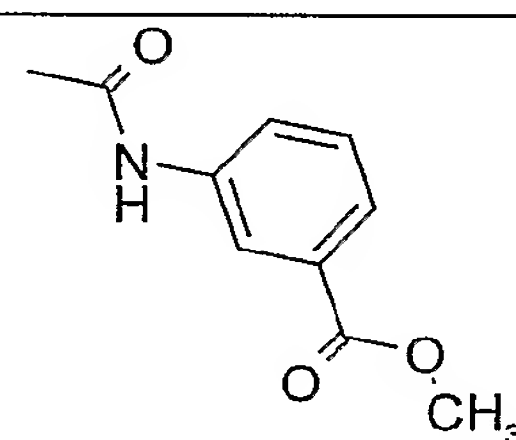
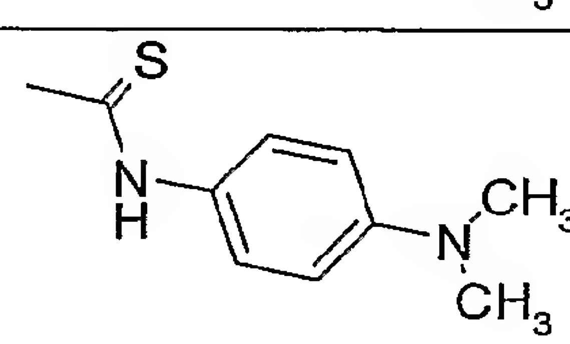
393	Benzenesulfonyl chloride		424.1826
394	1-Methylimidazole-4-sulfonyl chloride		428.1883
395	2,2,2-Trifluoroethanesulfonyl chloride		430.1515
396	3-Methylbenzenesulfonyl chloride		438.1981
397	*alpha*-Toluenesulfonyl chloride		438.1944
398	*p*-Toluenesulfonyl chloride		438.2003
399	3-Fluorobenzenesulfonyl chloride		442.1712
400	4-Fluorobenzenesulfonyl chloride		442.1740
401	3-Cyanobenzenesulfonyl chloride		449.1736

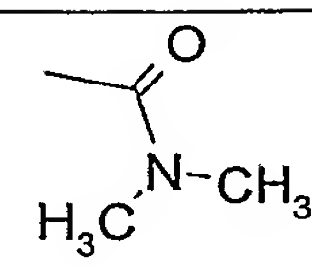
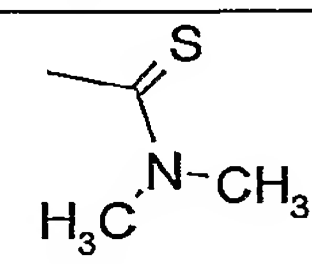
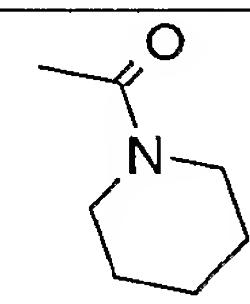
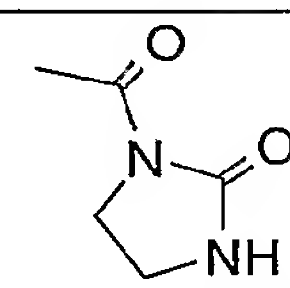
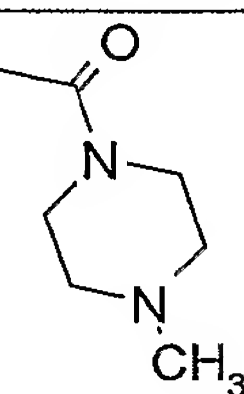
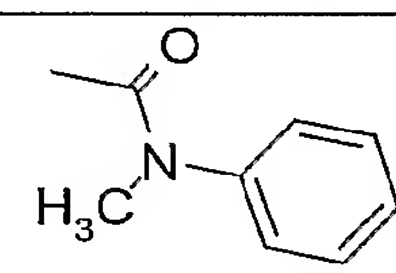
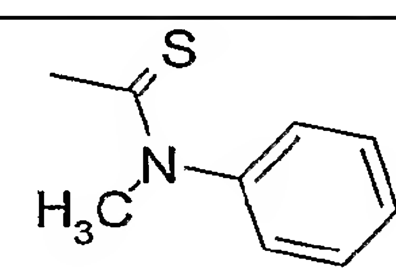
402	4-Cyanobenzenesulfonyl chloride		449.1800
403	*beta*-Styrenesulfonyl chloride		450.1969
404	3-Methoxybenzenesulfonyl chloride		454.1942
405	4-Methoxybenzenensulfonyl chloride		454.1910
406	2-Chlorobenzenesulfonyl chloride		458.1417
407	3-Chlorobenzenesulfonyl chloride		458.1423
408	4-Chlorobenzenesulfonyl chloride		458.1418

409	2-Naphthalenesulfonyl chloride		474.1969
410	3,4-Dichlorobenzenesulfonyl chloride		492.1036
411	10-Camphorsulfonyl chloride		498.2510
412	3-(Trifluoromethoxy)benzenesulphonyl chloride		508.1635
413	Methyl isocyanate		341.2076
414	Ethyl isocyanate		355.2278
415	Methyl isothiocyanate		357.1883
416	Isopropyl isocyanate		369.2388
417	Ethyl isothiocyanate		371.2035
418	Cyclopropyl isothiocyanate		383.2018

419	Isopropyl isothiocyanate		385.2171
420	Pentyl isocyanate		397.2738
421	Cyclopropyl isothiocyanate		397.2174
422	Isobutyl isothiocyanate		399.2336
423	Phenyl isocyanate		403.2256
424	Cyclohexyl isocyanate		409.2725
425	Benzyl isocyanate		417.2388
426	*m*-Tolyl isocyanate		417.2409
427	*o*-Tolyl isocyanate		417.2403
428	*p*-Tolyl isocyanate		417.2428

429	Phenyl isothiocyanate		419.2035
430	3-Pyridyl isothiocyanate		420.1951
431	Benzoyl isocyanate		431.2180
432	2-Phenylethyl isocyanate		431.2529
433	2-Methoxyphenyl isocyanate		433.2350
434	3- Methoxyphenyl isocyanate		433.2338
435	4- Methoxyphenyl isocyanate		433.2359
436	2-(Thien-2-yl)ethyl isocyanate		437.2132
437	2-Chlorophenyl isocyanate		437.1870

438	3-Chlorophenyl isocyanate		437.1870
439	4- Chlorophenyl isocyanate		437.1896
440	3,4-Difluorophenyl isocyanate		439.2064
441	*trans*-2-Phenylcyclopropyl isocyanate		443.2563
442	3-Cyanophenyl isothiocyanate		444.1997
443	3-Acetylphenyl isocyanate		445.2336
444	2-Morpholinoethyl isothiocyanate		456.2535
445	3-Carbomethoxyphenyl isocyanate		461.2263
446	4-(Dimethylamino)phenyl isocyanate		462.2433

447	*N,N*-Dimethylcarbamoyl chloride		355.2226
448	Dimethylthiocarbamoyl chloride		371.2020
449	1-Piperidinecarbonyl chloride		395.2556
450	2-Oxo-1-imidazolidinecarbonyl chloride		396.2154
451	4-Methyl-1-piperazinecarbonyl chloride		410.2647
452	*N*-Methyl-*N*-phenylcarbamoyl chloride		417.2386
453	*N*-Methyl-*N*-phenylthiocarbamoyl chloride		433.2192

Example 454-488

Part A

Ethyl 5-(4-chlorobutyl)-1-methyl-1*H*-pyrazole-3-carboxylate was prepared from 6-chloro-2-hexanone (50.0 g, 357 mmol) and diethyl oxalate (48.4 mL, 357 mmol) according to the procedure described in Part A of Example 19 using methyl hydrazine (19.0 mL, 357 mmol) in place of ethylhydrazine oxalate. Ethyl 5-(4-chlorobutyl)-1-methyl-1*H*-pyrazole-3-carboxylate was isolated as a dark oil that was used without purification in the next step.

Part B

The material from Part A was converted into ethyl 5-[4-(acetyloxy)butyl]-1-methyl-1*H*-pyrazole-3-carboxylate according to the procedure used in Part B of Example 19. The crude product was used without purification in the next step.

Part C

A solution of the material from Part B in methanol (175 mL) was treated with ammonium hydroxide (250 mL) according to a modification of the method described in Part D of Examples 1-4. The reaction was heated overnight at 125 °C and allowed to cool to ambient temperature. The methanol and water were removed under reduced pressure. Acetonitrile was added and the mixture was filtered through a plug of silica gel (eluted with 20% methanol in chloroform). The filtrate was concentrated to yield 5-(4-hydroxybutyl)-1-methyl-1*H*-pyrazole-3-carboxamide that was used in the next step without further purification.

Part D

A modification of the method described in Part E of Examples 1-4 was used to treat 5-(4-hydroxybutyl)-1-methyl-1*H*-pyrazole-3-carboxamide (42.9 g, 218 mmol) with phosphorous oxychloride (130 mL). The reaction was heated for two hours at 90 °C before cooling to 0 °C and pouring into ice water. The mixture was adjusted to pH 12 with the addition of 2 N aqueous sodium carbonate and 50% aqueous sodium hydroxide. The mixture was extracted with chloroform. The combined extracts were passed through a layer of silica gel (eluting first with chloroform and then with ethyl acetate to provide 23.0 g of 5-(4-chlorobutyl)-1-methyl-1*H*-pyrazole-3-carbonitrile as a dark oil that was used in the next step without further purification.

Part E

A modification of the method described in Part E of Example 19 was used to convert the material from Part D (23.0 g) into 4-bromo-5-(4-chlorobutyl)-1-methyl-1*H*-pyrazole-3-carbonitrile. The reaction was allowed to stir for one day before an aqueous solution of sodium bisulfite was added to quench the excess bromine. The reaction was worked up as described for Part E of Example 19, except that after the combined organic layers were dried over sodium sulfate, they were passed through a plug of silica gel (eluted with 1:1 ethyl acetate/hexanes). The filtrate was concentrated and the crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 10-50% ethyl acetate/hexanes. The appropriate fractions were combined and concentrated to yield 7.3 g of 4-bromo-5-(4-chlorobutyl)-1-methyl-1*H*-pyrazole-3-carbonitrile as a clear oil.

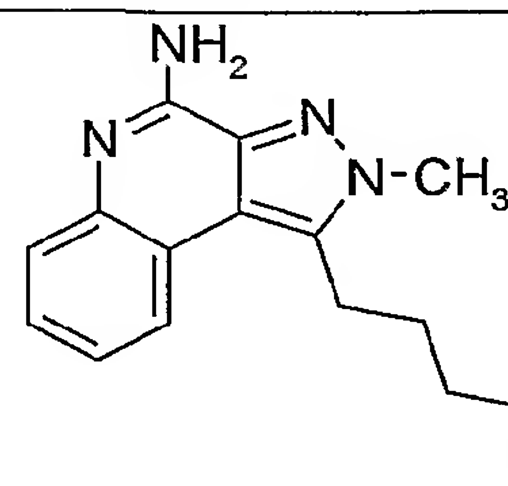
Part F

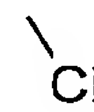
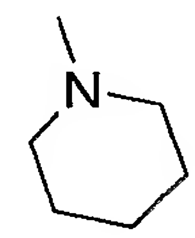
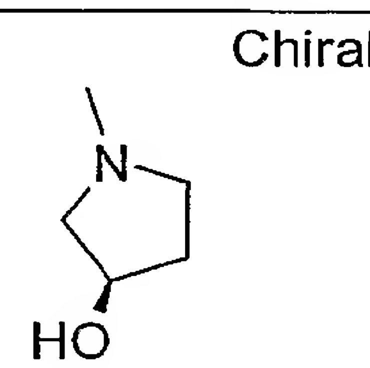
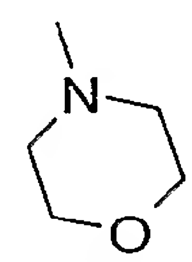
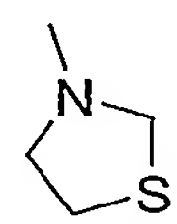
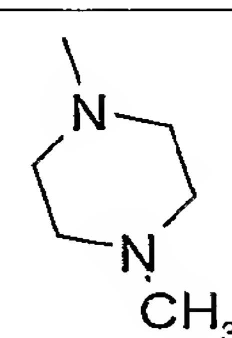
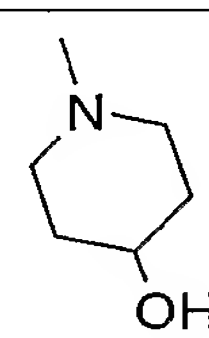
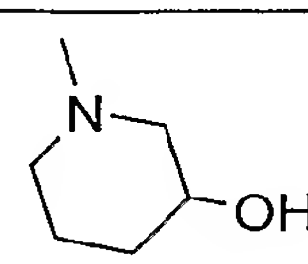
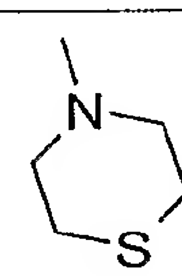
2-Aminophenylboronic acid hydrochloride (9.20 g, 53.0 mmol), potassium phosphate (28.0 g, 133 mmol), tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (685 mg, 0.662 mmol), and bis[(2-diphenylphosphino)phenyl]ether (428 mg, 0.795 mmol) were added to a mixture of 4-bromo-5-(4-chlorobutyl)-1-methyl-1*H*-pyrazole-3-carbonitrile (7.30 g, 26.5 mmol) and powdered molecular sieves (1 g) in toluene (165 mL). Nitrogen was bubbled through the reaction mixture, and then the reaction was heated at 110 °C for 24 hours. The mixture was filtered through a layer of silica gel (eluting with 3:2 chloroform/methanol). The filtrate was concentrated under reduced pressure and dissolved in ethanol (130 mL). Hydrogen chloride (20 mL of a 4 M solution in ethanol) was added to the solution and the reaction was heated at reflux for two hours and allowed to cool to ambient temperature. The reaction was worked up as described in Part F of Example 19. After purification by chromatography on a HORIZON HPFC system, the solid was stirred in acetonitrile and filtered to provide 1.0 g of 1-(4-chlorobutyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine that was used in the next step. The filtrate was concentrated to provide an additional 4.0 g of product.

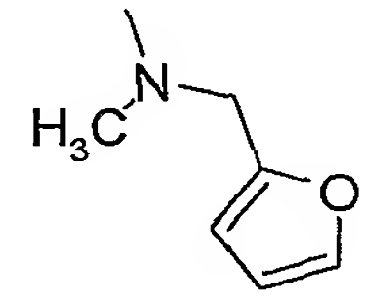
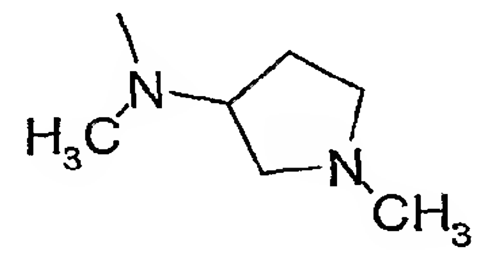
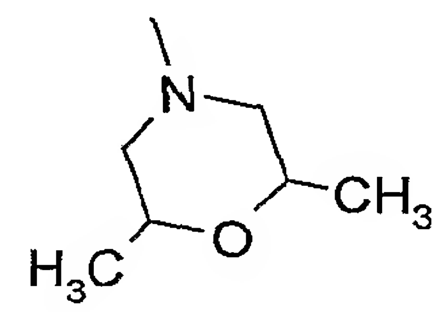
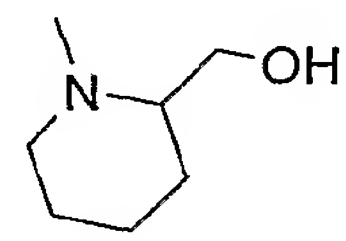
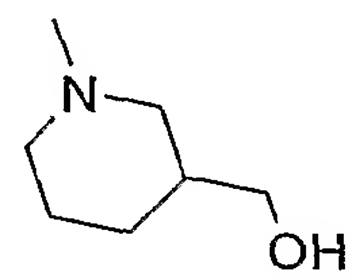
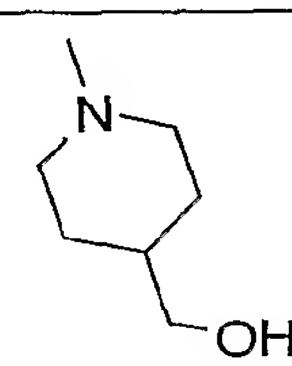
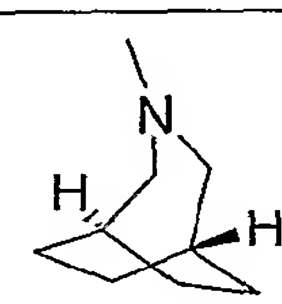
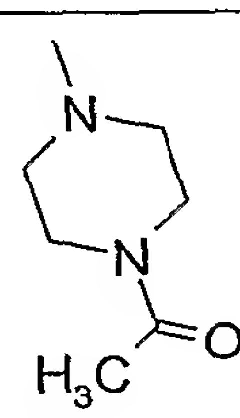
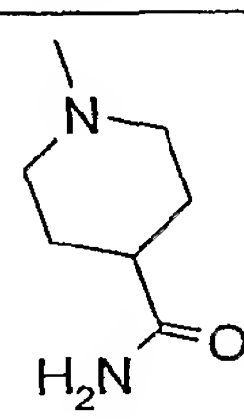
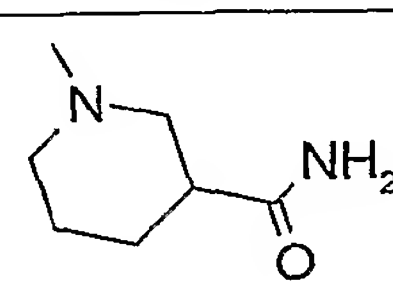
Part G

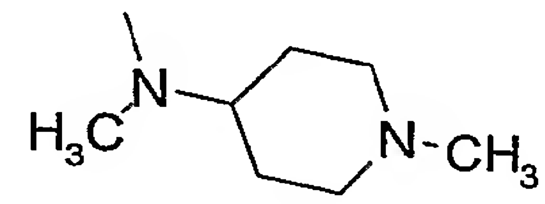
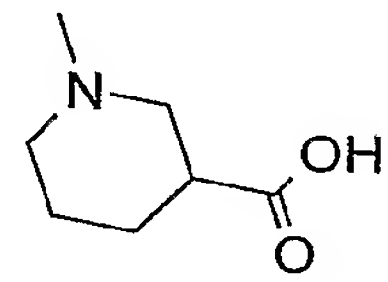
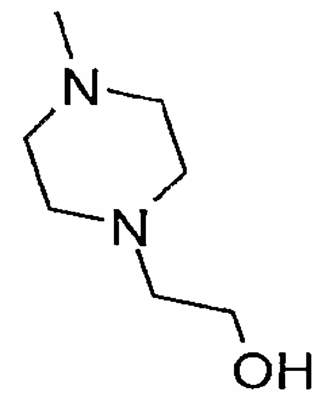
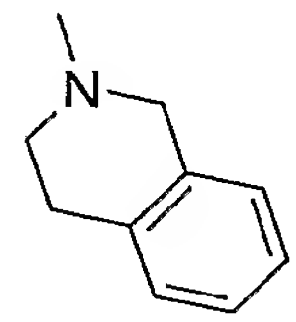
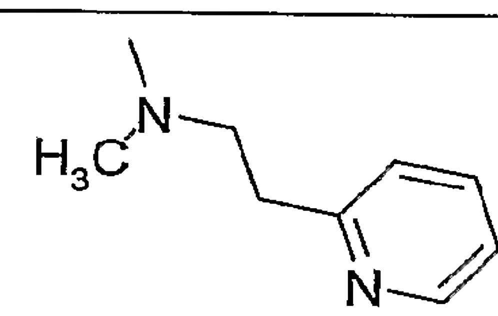
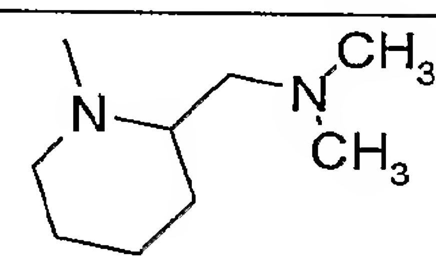
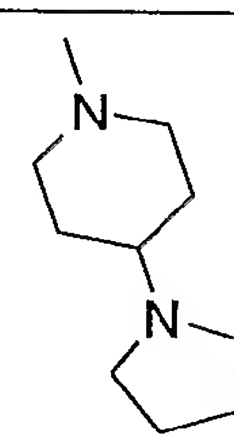
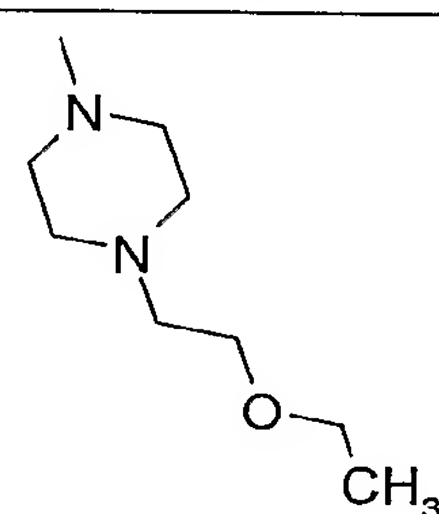
A reagent (0.15 mmol, 1.5 equivalents) from the table below was added to a test tube containing 1-(4-chlorobutyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (29 mg, 0.10 mmol) and potassium carbonate (approximately 55 mg, 0.40 mmol) in DMF (1 mL). The test tubes were capped and heated at 100 °C for approximately 22 hours. The reaction mixtures were filtered and the solvent was removed from the filtrates by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

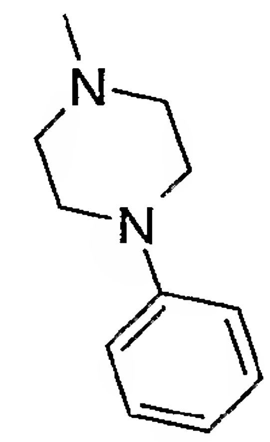
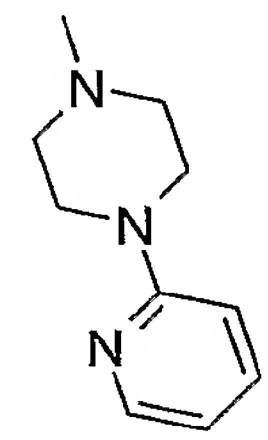
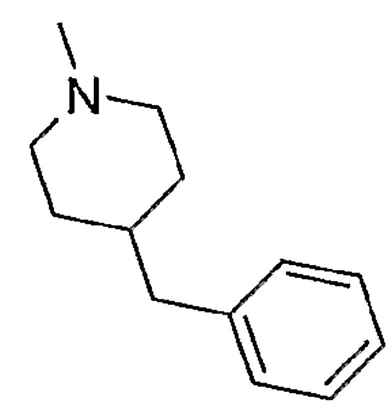
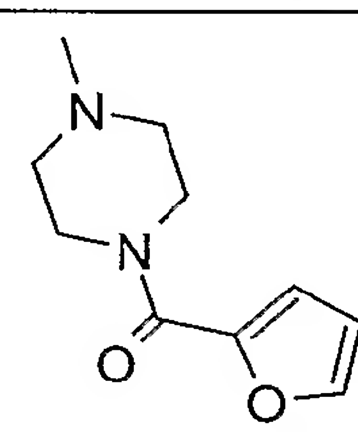
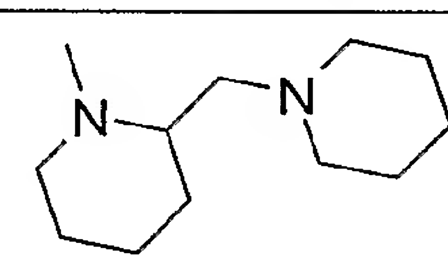
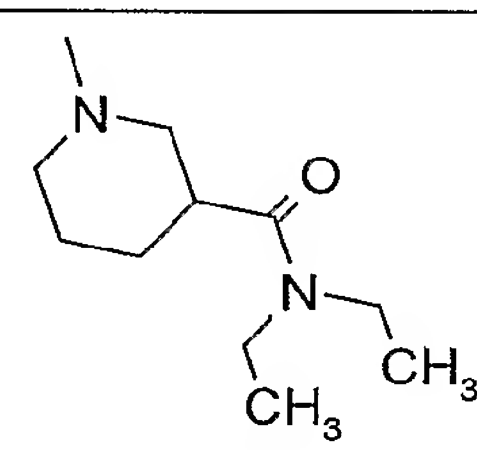
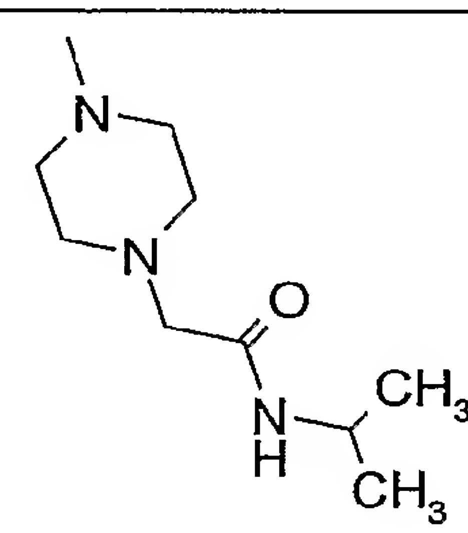
Examples 454-488

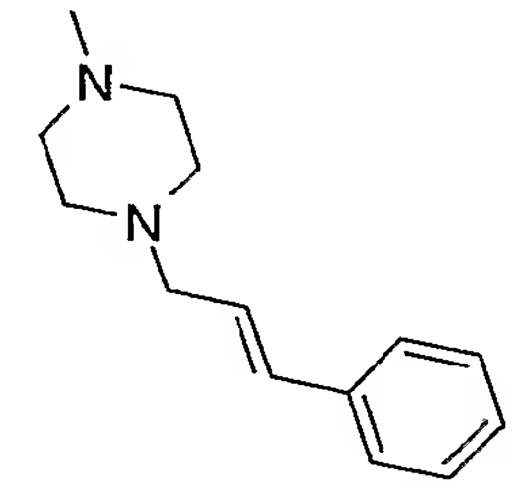


Example	Reagent	R	Measured Mass (M+H)
454	none		289.1205
455	Piperidine		338.2332
456	(R)-3-Hydroxypyrrolidine		340.2130
457	Morpholine		340.2120
458	Thiazolidine		342.1721
459	1-Methylpiperazine		353.2425
460	4-Hydroxypiperidine		354.2310
461	3- Hydroxypiperidine		354.2268
462	Thiomorpholine		356.1884

463	*N*-Methylfurfurylamine		364.2134
464	*N,N'*-Dimethyl-3-aminopyrrolidine		367.2619
465	2,6-Dimethylmorpholine		368.2448
466	2-Piperidinemethanol		368.2426
467	3-(Hydroxymethyl)piperidine		368.2443
468	4-(Hydroxymethyl)piperidine		368.2437
469	3-Azabicyclo[3.2.2]nonane		378.2622
470	1-Acetylpiperazine		381.2406
471	Isonipecotamide		381.2375
472	Nipecotamide		381.2426

473	1-Methyl-4-(methylamino)piperidine		381.2733
474	Nipecotic acid		382.2213
475	*N*-(2-Hydroxyethyl)piperazine		383.2571
476	1,2,3,4-Tetrahydroisoquinoline		386.2333
477	2-(2-Methylaminoethyl)pyridine		389.2438
478	*N*-(2-Piperidylmethyl)dimethylamine		395.2915
479	4-(1-Pyrrolidinyl)-piperidine		407.2894
480	1-(2-Ethoxyethyl)piperazine		411.2862

481	1-Phenylpiperazine		415.2572
482	1-(2-Pyrdiyl)piperazine		416.2568
483	4-Benzylpiperidine		428.2816
484	1-(2-Furoyl)piperazine		433.2371
485	2-Piperidin-1-ylmethyl-piperidine		435.3229
486	*N*,*N*-Diethylnipecotamide		437.3021
487	*N*-Isopropyl-1-piperazineacetamide		438.3000

488	1-Cinnamylpiperazine		455.2915

Example 489-518

Part A

Potassium phthalimide (4.90 mg, 26.4 mmol), sodium iodide (495 mg, 3.30 mmol), and DMF (22 mL) were added to 1-(4-chlorobutyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (4.00 g, 13.2 mmol, prepared as described in Parts A-F of Examples 454-489), and the reaction was heated at 90 °C for two hours under a nitrogen atmosphere and allowed to cool to ambient temperature. Water (100 mL) was added and a precipitate formed and was isolated by filtration to yield 3.7 g of 2-[4-(4-amino-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]-1*H*-isoindole-1,3(2*H*)-dione that was used in the next step.

Part B

A solution of the material from Part A (3.7 g, 8.9 mmol) and hydrazine hydrate (2.15 mL, 44.5 mmol) in ethanol (111 mL) was heated at reflux for 30 minutes, then was cooled to 0 °C and a white solid formed. The solid was isolated and washed with ethanol. The solid was combined with some material from another experiment and was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 5-50% CMA in chloroform). The appropriate fractions were combined, concentrated, and triturated with acetonitrile to afford a solid that was isolated by filtration to yield 880 mg of 1-(4-aminobutyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a tan powder.

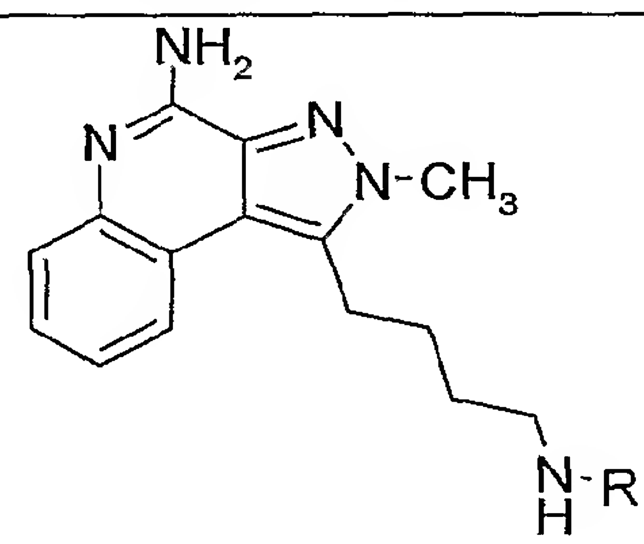
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (dd, J = 7.6, 1.2 Hz, 1H), 7.48 (dd, J = 7.6, 1.2 Hz, 1H), 7.31 (td, J = 7.2, 1.5 Hz, 1H), 7.19 (td, J = 8.1, 1.4 Hz, 1H), 6.62 (br s, 2H), 4.10 (s, 3H), 3.31 (s, 2H), 3.23 (t, J = 7.6 Hz, 2H), 2.57 (t, J = 6.9 Hz, 2H), 1.71 (m, 2H), 1.49 (m, 2H);

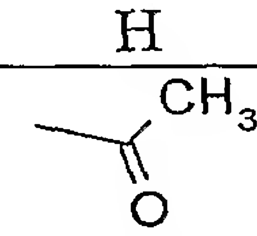
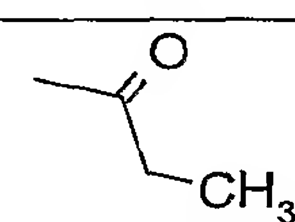
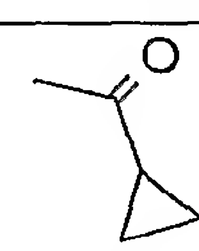
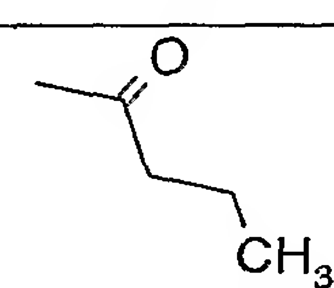
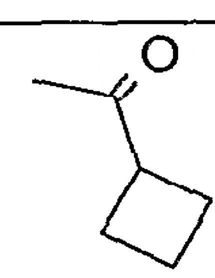
MS (APCI) m/z 270 $(M + H)^+$.

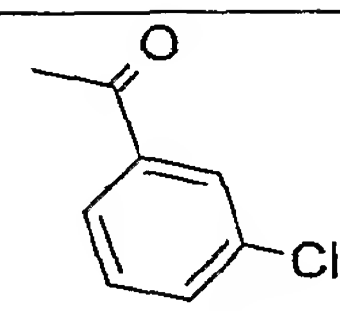
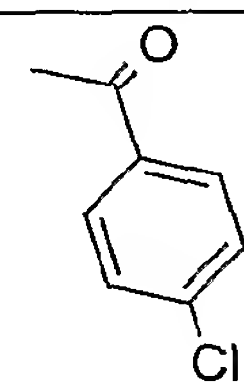
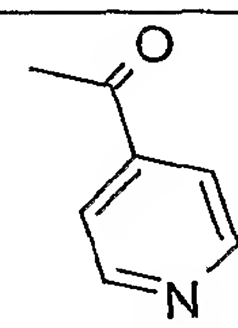
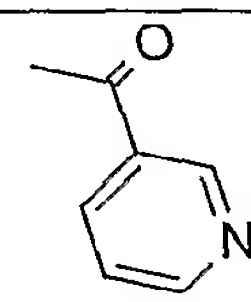
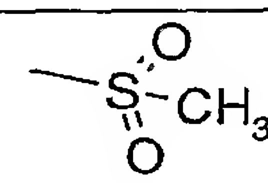
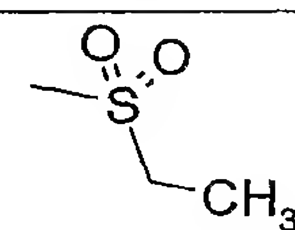
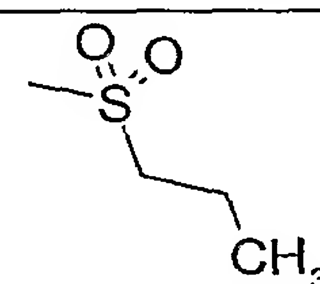
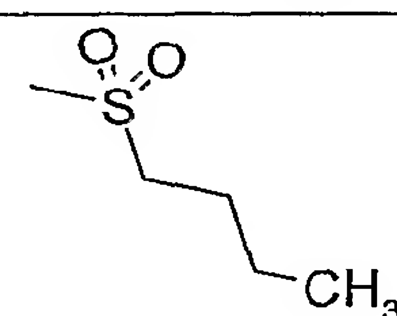
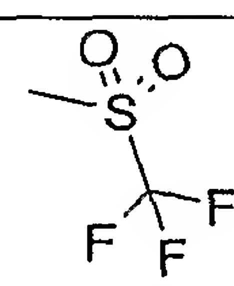
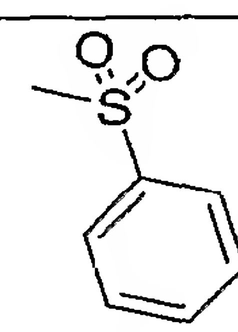
Part C

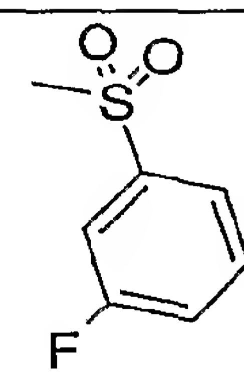
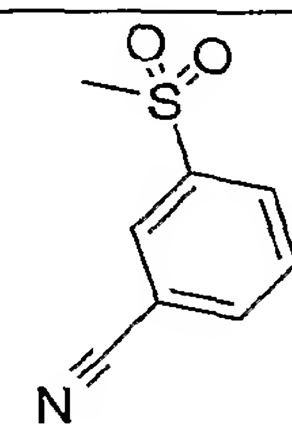
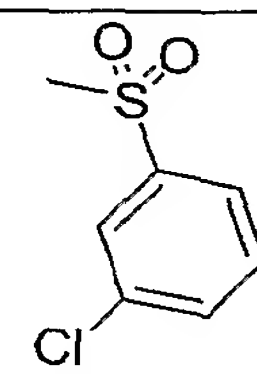
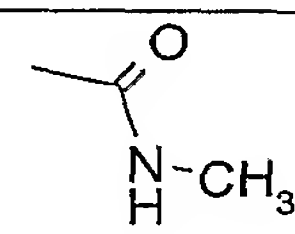
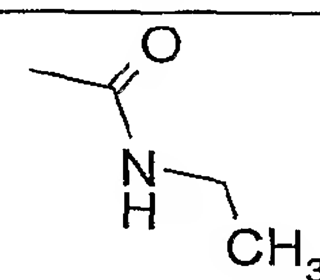
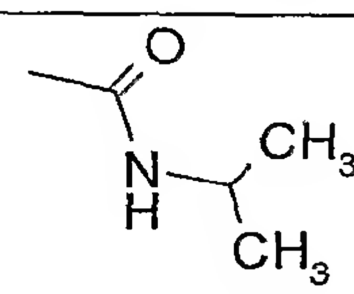
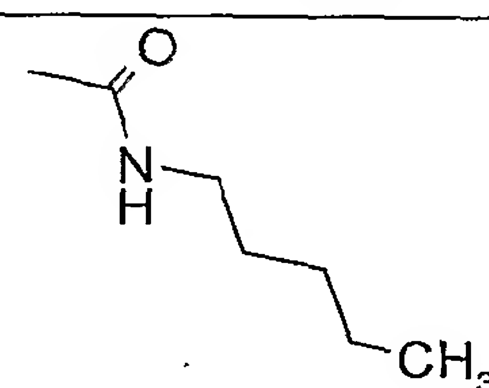
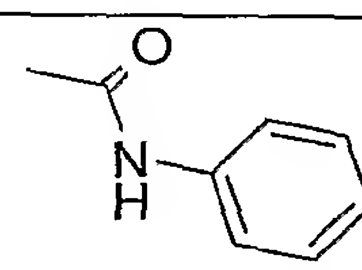
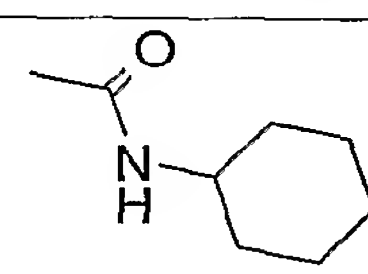
A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(4-aminobutyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (27 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (0.033 mL, 0.20 mmol) in chloroform (1 mL). The test tubes were capped and shaken overnight at room temperature and then two drops of water were added to each test tube. The solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

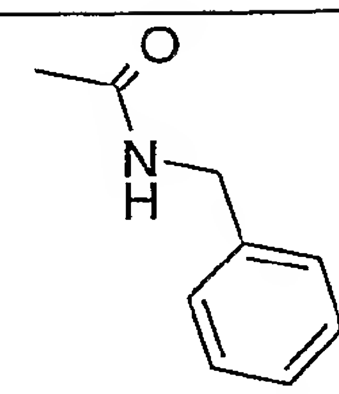
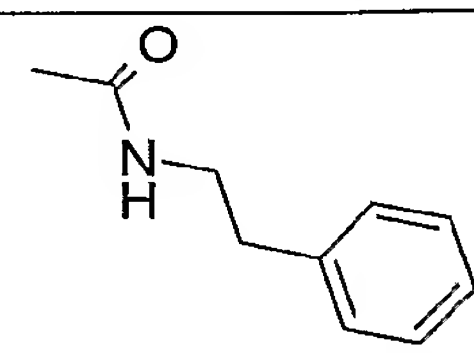
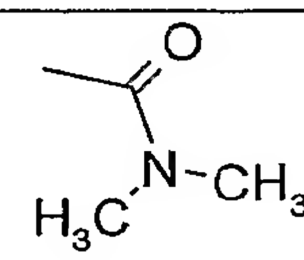
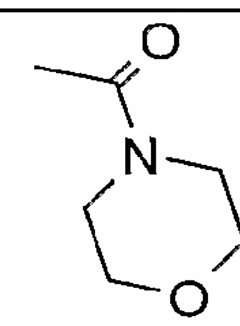
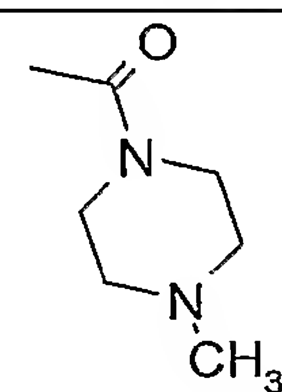
Examples 489-518



Example	Reagent	R	Measured Mass (M+H)
489	none	H	270.1720
490	Acetyl chloride		312.1822
491	Propionyl chloride		326.1971
492	Cyclopropanecarbonyl chloride		338.1985
493	Butyryl chloride		340.2134
494	Cyclobutanecarbonyl chloride		352.2128

495	3-Chlorobenzoyl chloride		408.1593
496	4-Chlorobenzoyl chloride		408.1610
497	Isonicotinoyl chloride hydrochloride		375.1924
498	Nicotinoyl chloride hydrochloride		375.1945
499	Methanesulfonyl chloride		348.1503
500	Ethanesulfonyl chloride		362.1656
501	1-Propanesulfonyl chloride		376.1838
502	1-Butanesulfonyl chloride		390.1973
503	Trifluoromethanesulfonyl chloride		402.1238
504	Benzenesulfonyl chloride		410.1693

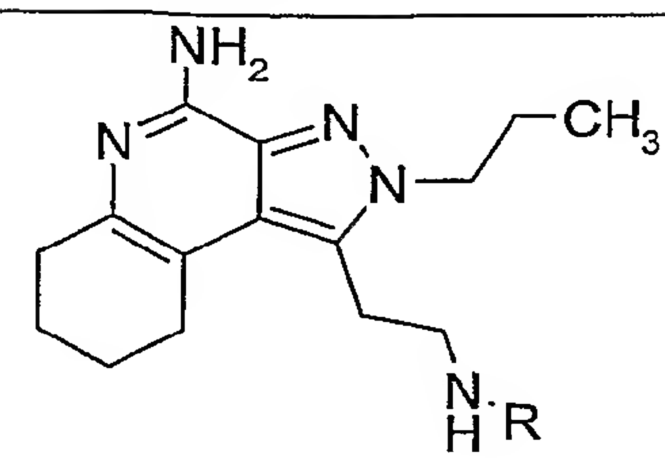
505	3-Fluorobenzenesulfonyl chloride		428.1566
506	3-Cyanobenzenesulfonyl chloride		435.1588
507	3-Chlorobenzenesulfonyl chloride		444.1227
508	Methyl isocyanate		327.1951
509	Ethyl isocyanate		341.2088
510	Isopropyl isocyanate		355.2279
511	Pentyl isocyanate		383.2570
512	Phenyl isocyanate		389.2083
513	Cyclohexyl isocyanate		395.2576

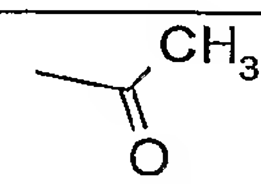
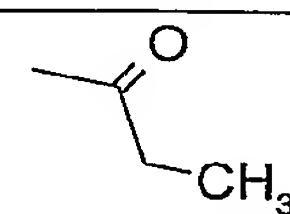
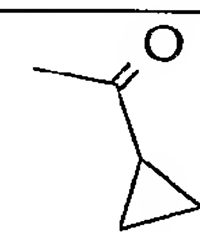
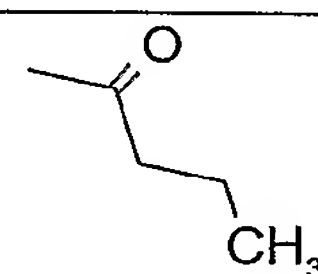
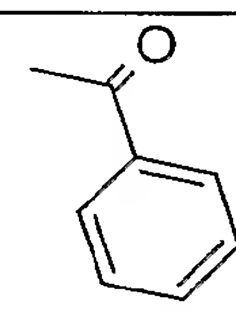
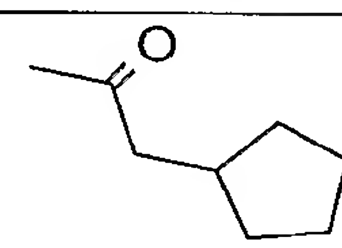
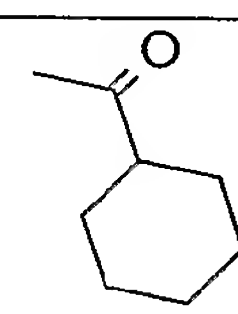
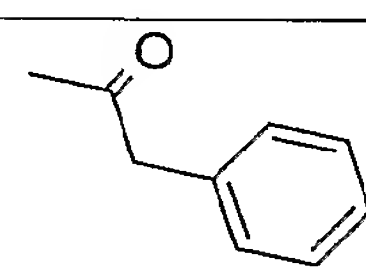
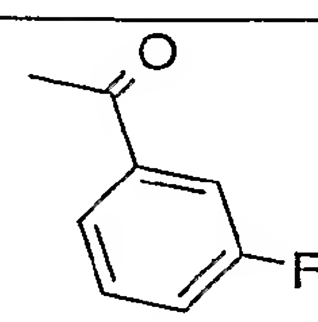
514	Benzyl isocyanate		403.2261
515	2-Phenylethyl isocyanate		417.2420
516	*N,N*-Dimethylcarbamoyl chloride		341.2114
517	4-Morpholinylcarbonyl chloride		383.2235
518	4-Methyl-1-piperazinecarbonyl chloride		396.2516

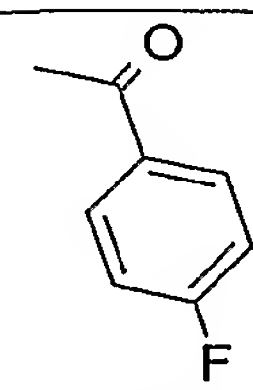
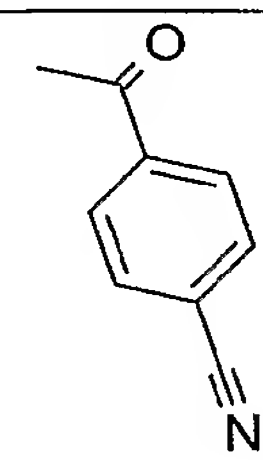
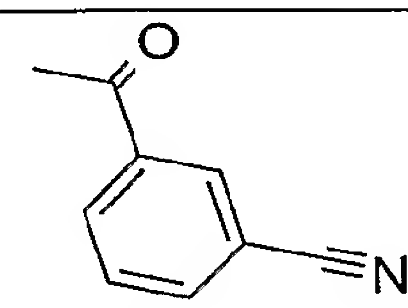
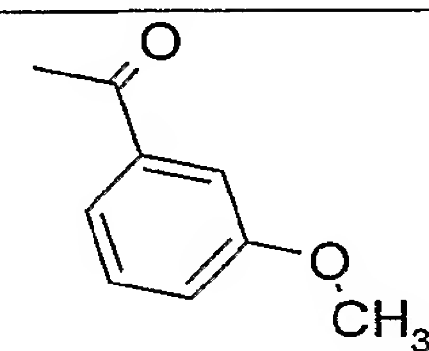
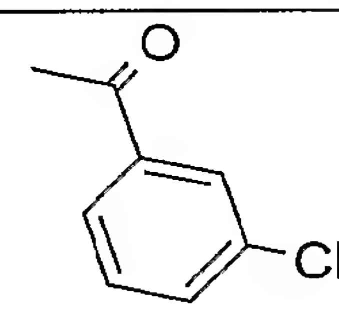
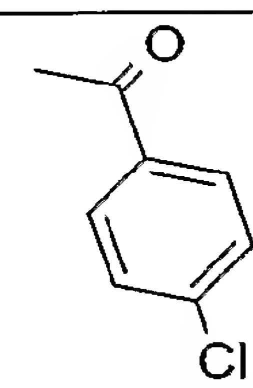
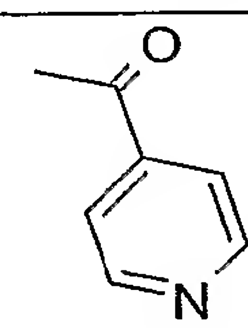
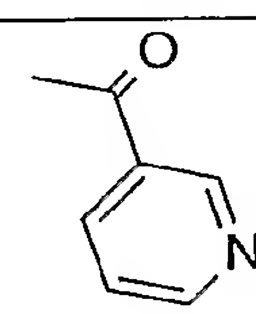
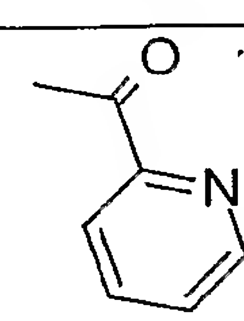
Examples 519-572

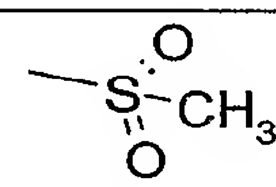
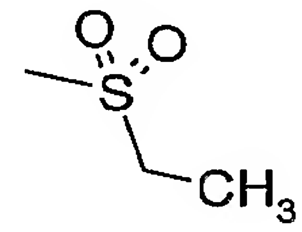
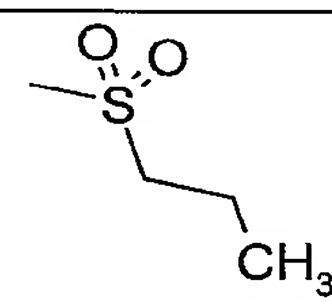
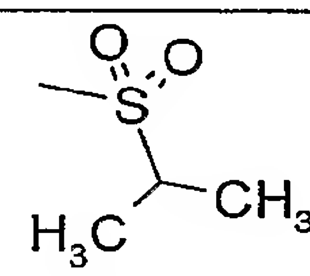
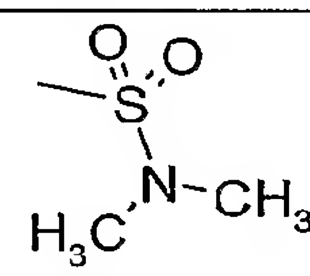
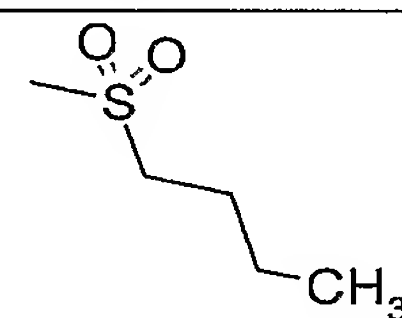
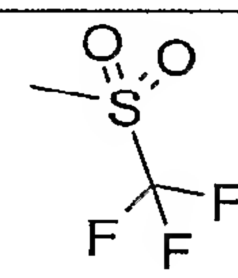
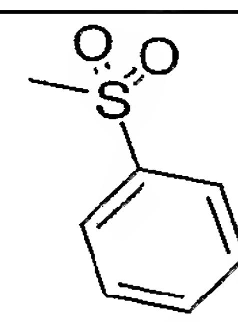
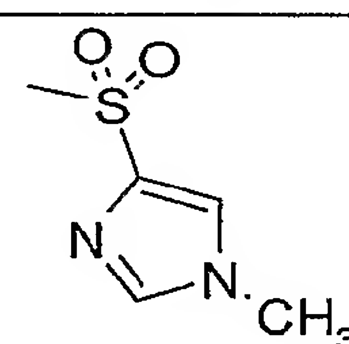
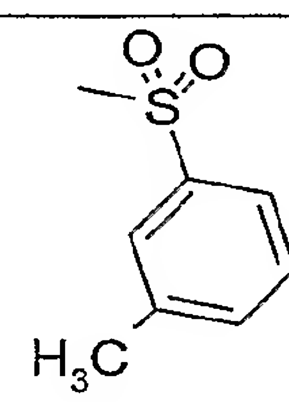
A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing the *bis*-trifluoroacetic acid salt of 1-(2-aminoethyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (50 mg, 0.10 mmol, prepared as described in Example 51) and *N,N*-diisopropylethylamine (0.070 mL, 0.40 mmol) in chloroform (1 mL). The test tubes were capped and shaken overnight at room temperature and then two drops of water were added to each test tube. The solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

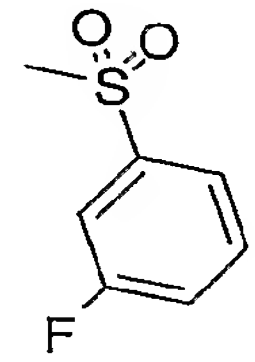
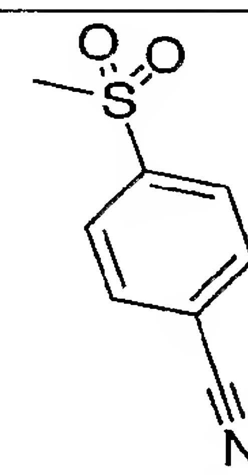
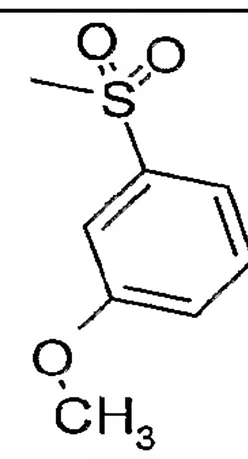
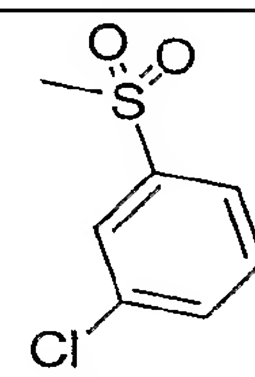
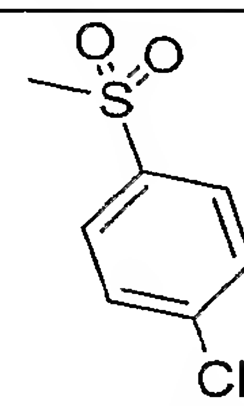
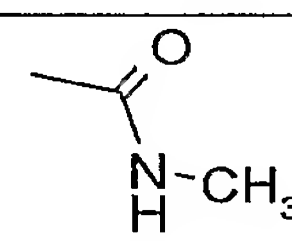
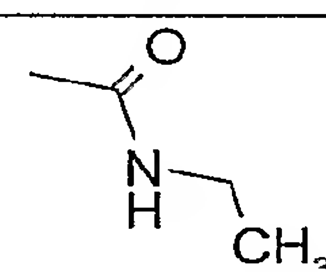
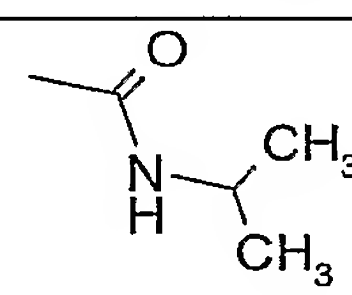
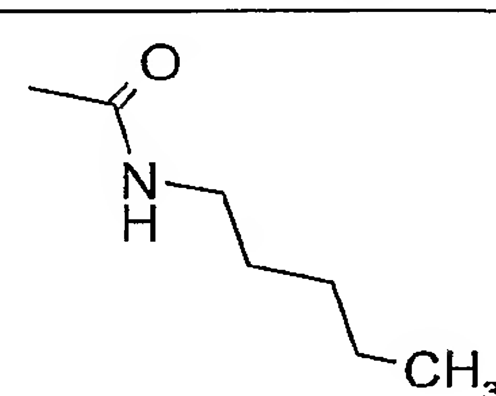
Examples 519-572

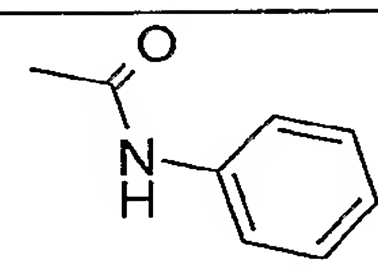
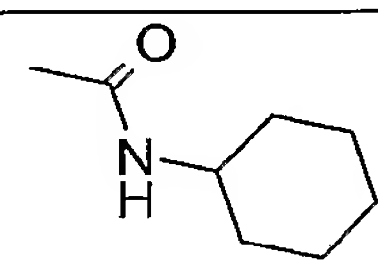
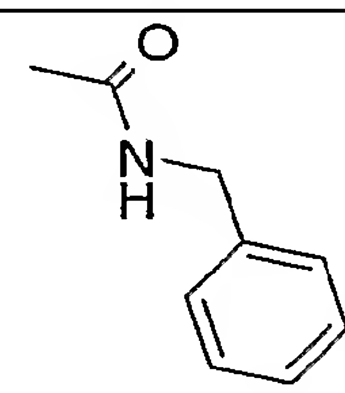
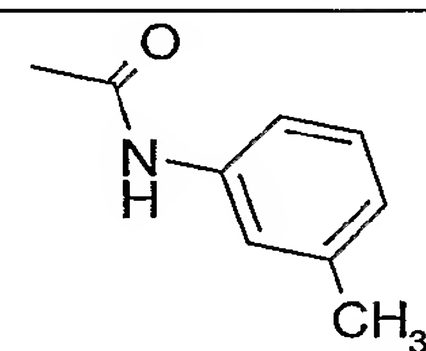
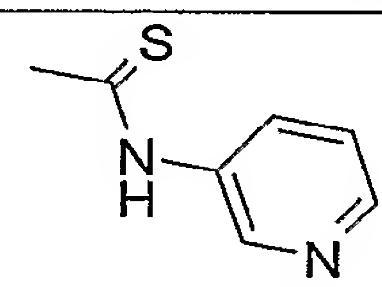
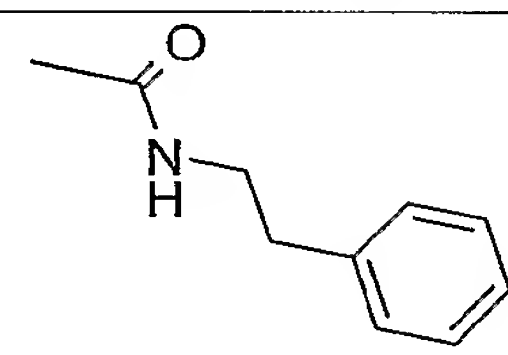
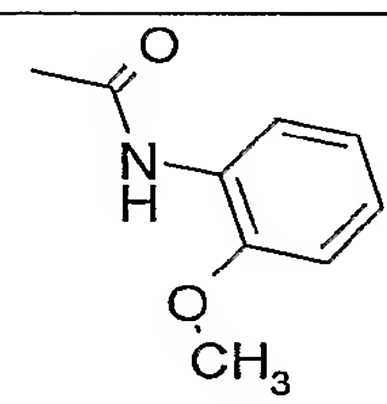
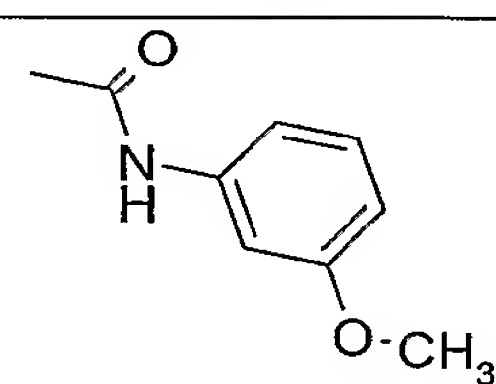
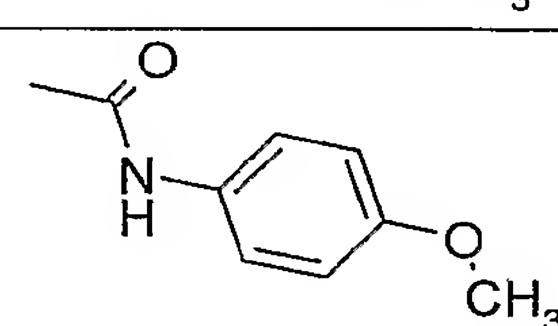


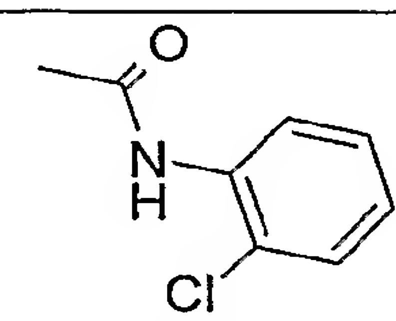
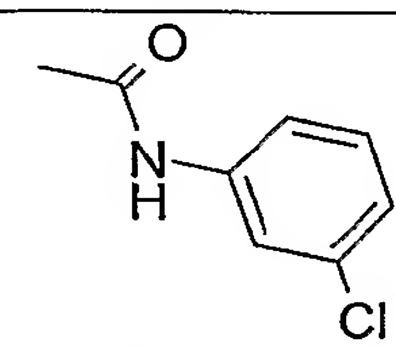
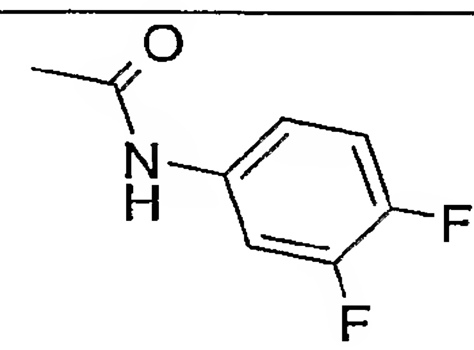
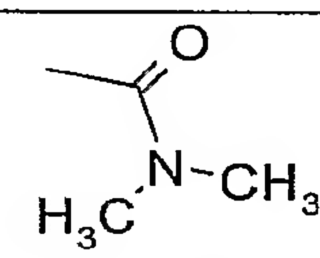
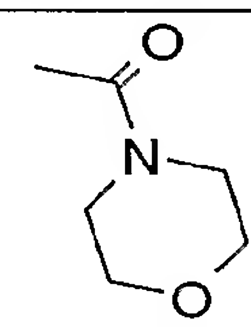
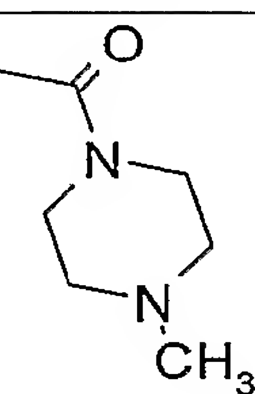
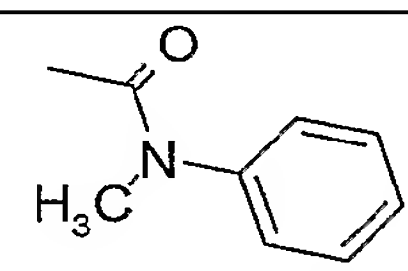
Example	Reagent	R	Measured Mass (M+H)
519	none	H	274.2038
520	Acetyl chloride		316.2154
521	Propionyl chloride		330.2310
522	Cyclopropanecarbonyl chloride		342.2291
523	Butyryl chloride		344.2472
524	Benzoyl chloride		378.2303
525	Cyclopentylacetyl chloride		384.2774
526	Cyclohexanecarbonyl chloride		384.2748
527	Phenylacetyl chloride		392.2445
528	3-Fluorobenzoyl chloride		396.2219

529	4-Fluorobenzoyl chloride		396.2224
530	4-Cyanobenzoyl chloride		403.2255
531	3-Cyanobenzoyl chloride		403.2243
532	3-Methoxybenzoyl chloride		408.2416
533	3-Chlorobenzoyl chloride		412.1931
534	4-Chlorobenzoyl chloride		412.1929
535	Isonicotinoyl chloride hydrochloride		379.2278
536	Nicotinoyl chloride hydrochloride		379.2258
537	Picolinoyl chloride hydrochloride		379.2265

538	Methanesulfonyl chloride		352.1819
539	Ethanesulfonyl chloride		366.1990
540	1-Propanesulfonyl chloride		380.2133
541	Isopropylsulfonyl chloride		380.2134
542	Dimethylsulfamoyl chloride		381.2080
543	1-Butanesulfonyl chloride		394.2316
544	Trifluoromethanesulfonyl chloride		406.1540
545	Benzenesulfonyl chloride		414.1985
546	1-Methylimidazole-4-sulfonyl chloride		418.2029
547	3-Methylbenzenesulfonyl chloride		428.2123

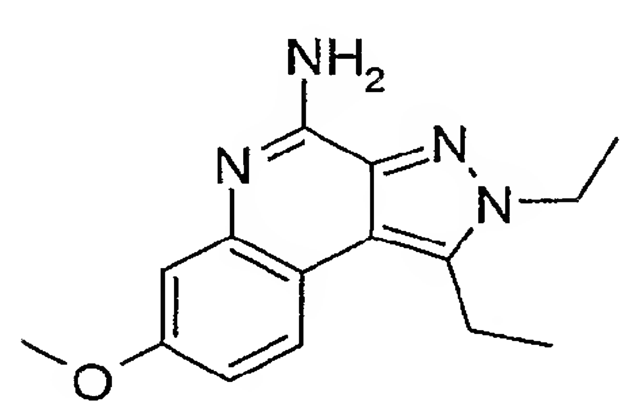
548	3-Fluorobenzenesulfonyl chloride		432.1890
549	4-Cyanobenzenesulfonyl chloride		439.1953
550	3-Methoxybenzenesulfonyl chloride		444.2095
551	3-Chlorobenzenesulfonyl chloride		448.1604
552	4-Chlorobenzenesulfonyl chloride		448.1575
553	Methyl isocyanate		331.2267
554	Ethyl isocyanate		345.2419
555	Isopropyl isocyanate		359.2592
556	Pentyl isocyanate		387.2903

557	Phenyl isocyanate		393.2431
558	Cyclohexyl isocyanate		399.2892
559	Benzyl isocyanate		407.2554
560	*m*-Tolyl isocyanate		407.2596
561	3-Pyridyl isothiocycante		410.2142
562	2-Phenylethyl isocyanate		421.2730
563	2-Methoxylphenyl isocyanate		423.2517
564	3-Methoxyphenyl isocyanate		423.2527
565	4-Methoxyphenyl isocyanate		423.2525

566	2-Chlorophenyl isocyanate		427.2018
567	3-Chlorophenyl isocyanate		427.2028
568	3,4-Difluorophenyl isocyanate		429.2248
569	*N,N*-Dimethylcarbamoyl chloride		345.2408
570	4-Morpholinylcarbonyl chloride		387.2500
571	4-Methyl-1-piperazinecarbonyl chloride		400.2845
572	*N*-Methyl-*N*-phenylcarbamoyl chloride		407.2571

Example 573

1,2-Diethyl-7-methoxy-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

To a stirred solution of *N*-(2-bromo-5-methoxyphenyl)-2,2-dimethylpropanamide (2.82 g, 9.85 mmol) in tetrahydrofuran (20 mL) at –78 °C was added slowly a solution of *n*-butyllithium in hexanes (2.5 M, 8.30 mL, 20.7 mmol). The solution was stirred for 30 minutes in a –40 °C bath, then was cooled back to –78 °C. Triisopropyl borate (6.82 mL, 29.6 mmol) was added slowly. The solution was stirred for 1 hour at –40 °C, then was stirred at 0 °C for 30 minutes. Saturated aqueous ammonium chloride was added. The mixture was extracted with diethyl ether. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated to afford a residue that was triturated with hexanes. The hexanes were decanted and the residue was stirred in methanol/water to precipitate a white solid that was isolated by filtration, washed with water, and dried to yield 1.36 g of 2-[(2,2-dimethylpropanoyl)amino]-4-methoxyphenylboronic acid, m.p. 256-257 °C. The material was used in the next step without further purification.

Part B

A 50 mL round bottom flask containing a mixture of 4-bromo-1,5-diethyl-1*H*-pyrazole-3-carbonitrile (prepared as described in Part E of Example 11, 1.12 g, 4.91 mmol) and 2-[(2,2-dimethylpropanoyl)amino]-4-methoxyphenylboronic acid (1.36 g, 5.40 mmol) in 1-propanol (25 mL) was evacuated and backfilled with nitrogen. To the flask was added triphenylphosphine (38.6 mg, 0.147 mmol), 2 M aqueous sodium carbonate (7.4 mL), water (5 mL), and palladium (II) acetate (11 mg, 0.048 mmol). The yellow suspension was heated at 100 °C. After 3 hours, the reaction mixture was allowed to cool to room temperature, water (10 mL) was added, and the 1-propanol was removed under reduced pressure. The water layer was extracted with ethyl acetate (2 x 30 mL). The organic layers were combined, washed with 2 M aqueous sodium carbonate (50 mL), water (50 mL), and brine (50 mL), then dried over sodium sulfate. The organic layer was concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-40% ethyl acetate in hexanes) to provide 0.54 g of *N*-[2-(3-cyano-1,5-diethyl-1*H*-pyrazol-4-yl)-5-methoxyphenyl]-2,2-dimethylpropanamide as a colorless liquid.

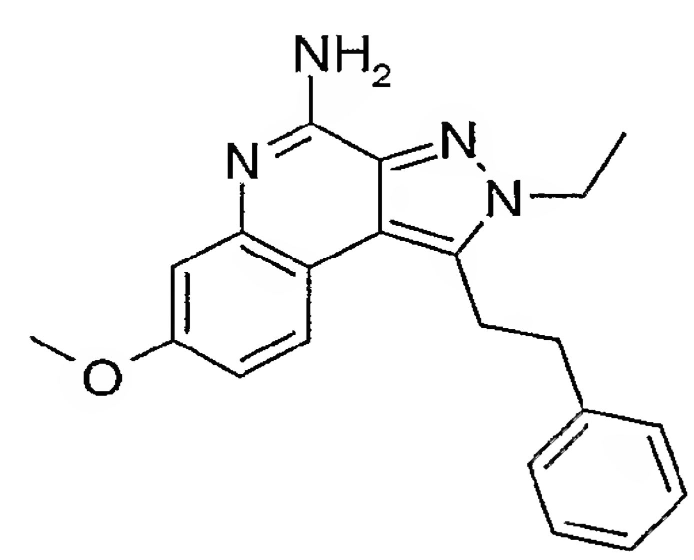
MS (ESI) *m/z* 355.28 $(M+H)^+$

Part C

A solution of sodium ethoxide in ethanol (21% by weight, 2.29 mL, 13.9 mmol) was added to a solution of *N*-[2-(3-cyano-1,5-diethyl-1*H*-pyrazol-4-yl)-5-methoxyphenyl]-2,2-dimethylpropanamide (0.5 g, 1.41 mmol) in ethanol (10 mL). The reaction mixture was stirred at room temperature for 20 minutes and then heated at reflux overnight. The reaction mixture was allowed to cool to room temperature and was concentrated under reduced pressure. The resulting residue was triturated with water to provide a solid that was isolated by filtration, washed with water, and dried. The material was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-20% CMA in chloroform) followed by crystallization from acetonitrile to yield 0.23 g of 1,2-diethyl-7-methoxy-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as beige needles, mp 210-211 °C.
^{1}H NMR (500 MHz, DMSO-d6) δ 7.8 (d, J = 8.7 Hz, 1H), 7.0 (d, J = 2.7 Hz, 1H), 6.80 (dd, J = 8.6, 2.7 Hz, 1H), 7.00 (s, 2H), 4.40 (q, J = 7.2 Hz, 2H), 3.80 (s, 1H), 3.21(q, J = 7.5 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H);
^{13}C-NMR (75 MHz, $CDCl_3$) δ158.0, 151.4, 145.6, 137.9, 135.3, 122.8, 116.8, 113.6, 110.6, 108.7, 55.3, 44.7, 18.6, 16.4, 13.6;
MS (ESI) *m/z* 271.2 $(M+H)^+$;
Anal. calcd for $C_{15}H_{18}N_4O$: C, 66.65; H, 6.71; N, 20.73. Found: C, 66.27; H, 6.59; N, 20.72.

Example 574

2-Ethyl-7-methoxy-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Using a modification on the method described in Part B of Example 573, 4-bromo-1-ethyl-5-(2-phenylethyl)-1*H*-pyrazole-3-carbonitrile (prepared as described in Part E of

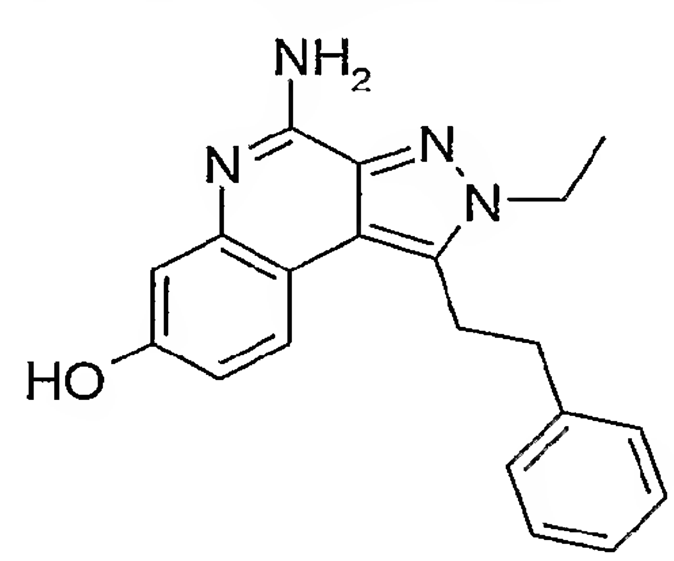
Example 41, 10.3 g, 33.9 mmol) was coupled with 2-[(2,2-dimethylpropanoyl)amino]-4-methoxyphenylboronic acid (prepared as described in Part A of Example 573, 15.3 g, 60.9 mmol). The reaction was worked up and purified as described in Part B of Example 573 to yield 1.7 g of *N*-{2-[3-cyano-1-ethyl-5-(2-phenylethyl)-1*H*-pyrazol-4-yl]-5-methoxyphenyl}-2,2-dimethylpropanamide as a colorless liquid, MS (ESI) *m/z* 431.17 $(M+H)^+$.

Part B

A modification of the method described in Part C of Example 573 was used to convert the material from Part A into 2-ethyl-7-methoxy-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-30% CMA in chloroform) followed by crystallization from acetonitrile to yield 0.57 g of 2-ethyl-7-methoxy-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as an off-white solid, mp 162-163 °C. MS (ESI) *m/z* 347.32 $(M+H)^+$; Anal. calcd for $C_{21}H_{22}N_4O$: C, 72.81; H, 6.40; N, 16.17. Found: C, 72.60; H, 6.53; N, 16.32.

Example 575

4-Amino-2-ethyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-7-ol hydrochloride

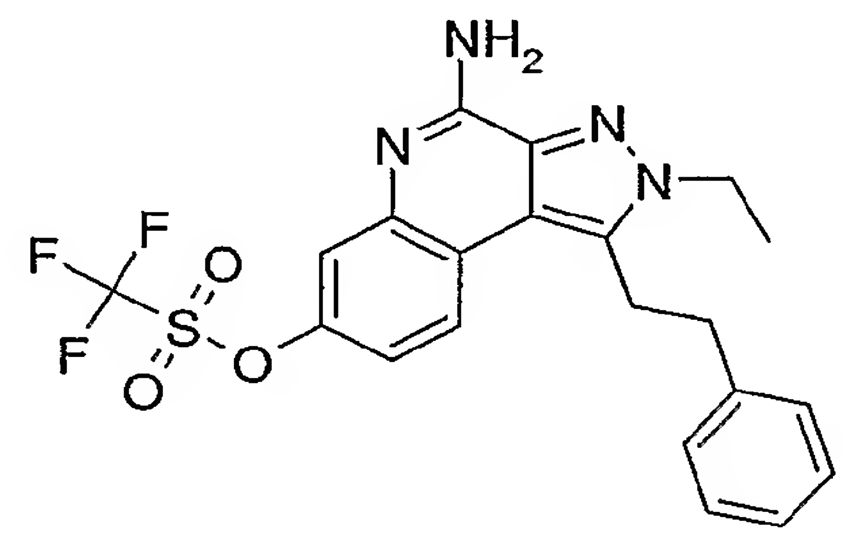


2-Ethyl-7-methoxy-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (0.37 g, 1.07 mmol) was added in one portion to boiling pyridinium chloride (3.70 g, 32.0 mmol). The mixture was heated at reflux for 4 hours, and then was allowed to cool to room temperature. The mixture was triturated with ice water and the precipitate was isolated by filtration, washed with water, and dried to yield 0.38 g of 4-amino-2-ethyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-7-ol hydrochloride as a light grey solid, mp >300 °C.

MS (ESI) m/z 333.31 $(M+H)^+$;
Anal. calcd for $C_{20}H_{20}N_4O{\bullet}1.1HCl{\bullet}0.25H_2O$: C, 63.72; H, 5.78; N, 14.86; Cl, 10.34. Found: C, 63.75; H, 5.96; N, 15.10; Cl, 10.61.

Example 576

4-Amino-2-ethyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-7-yl trifluoromethanesulfonate



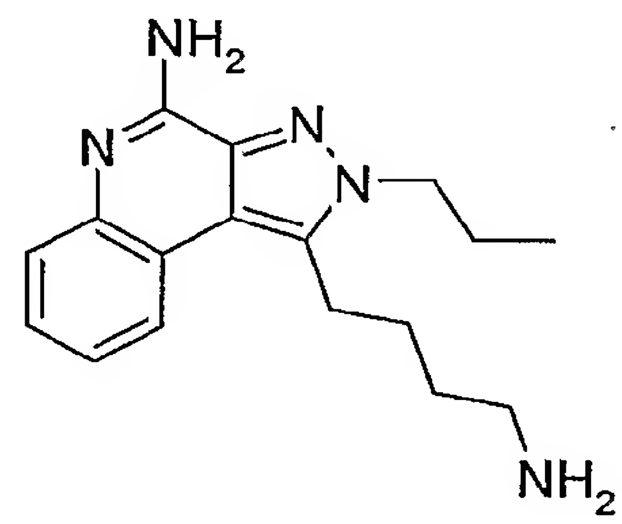
N-Phenyl-bis(trifluoromethanesulfonamide (0.187 g, 0.447 mmol) was added to a stirred solution of 4-amino-2-ethyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-7-ol hydrochloride (0.15 g, 0.41 mmol) and triethylamine (0.280 mL, 2.03 mmol) in DMF (5 mL). After 6 hours, water (25 mL) was added and a precipitate formed that was isolated by filtration, washed with water, and dried to yield 0.175 g of 4-amino-2-ethyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-7-yl trifluoromethanesulfonate as a white powder, mp 178-179 °C.

^{1}H NMR (300 MHz, DMSO-d6) δ 8.05 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.25 (m, 6H), 7.09 (s, 2H), 4.18 (q, J = 7.0 Hz, 2H), 3.54 (t, J = 7.3 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 1.32(t, J = 7.2 Hz, 3H).

MS (APCI) m/z 465.13 $(M+H)^+$.

Example 577

1-(4-Aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A mixture of potassium phthalimide (6.61 g, 35.7 mmol), sodium iodide (0.669 g, 4.46 mmol) and 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 46, 5.65 g, 17.8 mmol) in DMF (30 mL) was heated at 90 °C for 3 hours. The reaction mixture was allowed to cool to room temperature overnight, then was diluted with ice water (300 mL) and stirred for 10 minutes. A solid formed that was collected by filtration and dried to yield 7.14 g of 2-[4-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]-1*H*-isoindole-1,3(2*H*)-dione as a tan solid, mp 204-206 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86-7.70 (m, 5H), 7.69-7.64 (m, 1H), 7.43-7.36 (m, 1H), 7.29-7.22 (m, 1H), 5.37 (br s, 2H), 4.30 (t, J = 7.3 Hz, 2H), 3.77 (t, J = 6.8 Hz, 2H), 3.31-3.21 (m, 2H), 2.05-1.75 (m, 6H), 0.98 (t, J = 7.4 Hz, 3H).

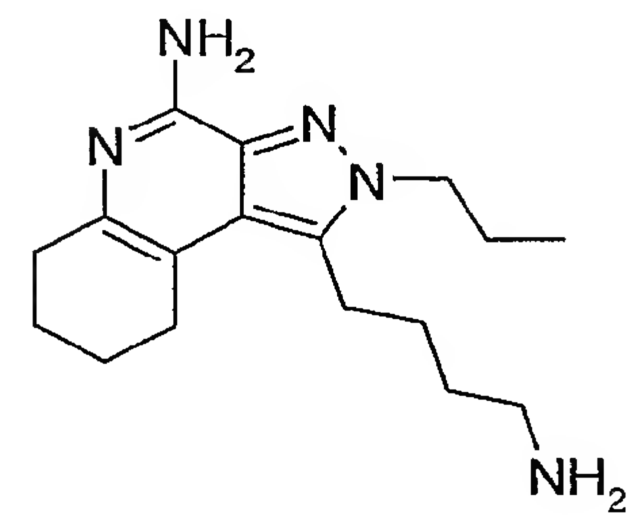
Part B

A mixture of 2-[4-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]-1*H*-isoindole-1,3(2*H*)-dione (7.21 g, 16.9 mmol) and hydrazine hydrate (4.22 g, 84.3 mmol) in ethanol (400 mL) was heated at reflux for 2 hours. The resulting solution was allowed to cool to room temperature, filtered, and concentrated under reduced pressure to yield 3.52 g of 1-(4-aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a yellow solid, mp 137-139 °C.

MS (APCI) m/z 298.2 $(M+H)^+$.

Example 578

1-(4-Aminobutyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



A solution of 1-(4-aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (2.40 g, 8.06 mmol) in trifluoroacetic acid (20 mL) was treated with platinum (IV) oxide. The mixture was hydrogenated on a Parr apparatus at 50 psi (3.5×10^5 Pa) for 1 day, and then was diluted with chloroform (50 mL) and methanol (25 mL). The mixture was filtered through CELITE filter agent. The filtrate was concentrated under reduced pressure to yield 6.0 g the *bis*-trifluoroacetic acid salt of 1-(4-aminobutyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine in residual trifluoroacetic acid as a yellow liquid.

MS (APCI) *m/z* 302.3 $(M+H)^+$.

Examples 579-581

Part A

A solution of 1-butyl-2-*tert*-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 43, 1.43 g, 4.60 mmol) in 6 M HCl in water (40 mL) was heated at 100 °C overnight. The reaction mixture was allowed too cool to room temperature and a white solid was isolated by filtration, washed with water to provide 1-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine hydrochloride that was used in the next step without extensive drying. Alternatively, the product can be dried in a vacuum oven at 95 °C. Anal. calcd for $C_{14}H_{16}N_4$•0.8 HCl: C, 56.31; H, 5.67; N, 18.76. Found: C, 56.64; H, 5.10; N, 18.68.

Part B

A solution of 1-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine hydrochloride (1 equivalent, 0.06 M), sodium *tert*-butoxide (3 equivalents), and an alkyl iodide from the

table below (3 equivalents) in ethanol was heated at reflux for 1-4 days. Additional alkyl iodide was added if necessary. The reaction mixture was allowed to cool to room temperature and a precipitate was isolated by filtration, washed with water, and dried. The crude product was purified by IFC (silica gel, gradient elution with CMA in chloroform). In Example 579, the product was further purified by precipitation from ethanol/water. In Examples 580 and 581, the product was further purified by reverse phase chromatography (gradient elution with acetonitrile in water containing 0.5% formic acid). In all examples, the final product was dried at 90 °C under vacuum.

Example 579: 1,2-Dibutyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was obtained as a white powder, mp 143.0–145.0 °C.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 7.89 (dd, J = 7.9, 1.1 Hz, 1H), 7.50 (dd, J = 8.1, 1.1 Hz, 1H), 7.33 (td, J = 7.2, 1.4 Hz, 1H), 7.22 (td, J = 8.0, 1.3 Hz, 1H), 6.59 (br s, 2H), 4.36 (t, J = 7.3 Hz, 2H), 3.23 (t, J = 8.1 Hz, 2H), 1.91-1.85 (m, 2H), 1.69-1.63 (m, 2H), 1.48 (sextet, J = 7.5 Hz, 2H), 1.36 (sextet, J = 7.6 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H);

MS (APCI) m/z 297 $(M + H)^+$;

Anal. calcd for $C_{18}H_{24}N_4$: C,72.94; H, 8.16; N, 18.90. Found: C, 72.70; H, 8.08; N, 19.05.

Example 580: The formic acid salt of 1-butyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was obtained as a white powder, mp 164–166 °C.

^{1}H NMR (700 MHz, DMSO-d$_6$) δ 8.17 (s, 0.8H), 7.90 – 7.89 (m, 1H), 7.50 – 7.49 (m, 1H), 7.34 – 7.31 (m, 1H), 7.23 - 7.21 (m, 1H), 6.83 (br s, 2H), 4.34 (t, J = 7 Hz, 2H), 3.23 (t, J = 7.6 Hz, 2H), 1.95 (sextet, J = 7.3 Hz, 2H), 1.67 (pentet, J = 7.9 Hz, 2H), 1.46 (sextet, J = 7.5 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H);

^{13}C NMR (175 MHz, DMSO) δ 163.34, 150.49, 143.04, 137.98, 135.33, 125.69, 125.12, 121.74, 121.65, 119.48, 116.25, 50.76, 30.62, 24.57, 23.53, 21.83, 13.66, 10.89;

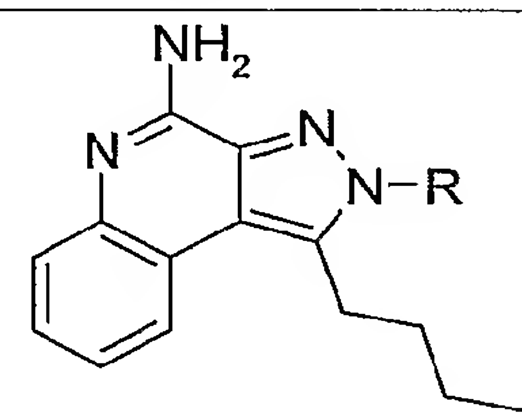
MS (APCI) m/z 283 $(M + H)^+$;

Anal. calcd for $C_{17}H_{22}N_4 \cdot 1.0\ CH_2O_2 \cdot 0.2\ H_2O$: C,65.12; H, 7.41; N, 16.87. Found: C, 64.73; H, 7.53; N, 16.92.

Example 581: The formic acid salt of 1-butyl-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine was obtained as a white powder, mp 202–203 °C.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.17 (s, 0.8H), 7.92 (dd, J = 7.9, 1.2 Hz, 1H), 7.50 (dd, J = 8.1, 1.1 Hz, 1H), 7.34 (td, J = 7.1, 1.4 Hz, 1H), 7.23 (td, J = 7.9, 1.3 Hz, 1H), 6.83 (br s, 2H), 4.10 (s, 3H), 3.23 (t, J = 7.6 Hz, 2H), 1.67 (pentet, J = 7.9 Hz, 2H), 1.46 (sextet, J = 7.5 Hz, 2H), 0.94 (t, J = 7.3 Hz, 3H);
^{13}C NMR (125 MHz, DMSO) δ 163.29, 150.38, 142.94, 138.15, 134.96, 125.70, 125.05, 121.73, 121.54, 119.39, 116.46, 37.23, 30.10, 24.67, 21.76, 13.62;
MS (APCI) m/z 255 $(M + H)^+$;
Anal. calcd for $C_{15}H_{18}N_4 \cdot 0.8\ CH_2O_2 \cdot 0.02\ H_2O$: C,65.10; H, 6.79; N, 19.22. Found: C, 64.75; H, 6.74; N, 19.22.

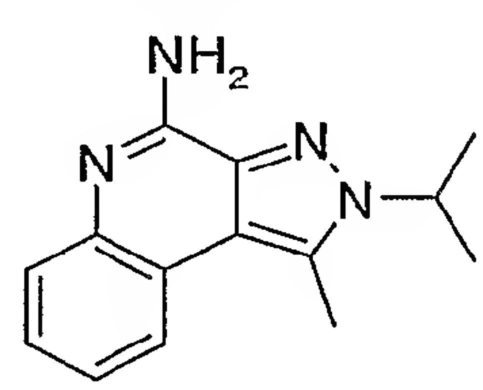
Examples 579-581



Example	Alkylating agent in Part B	R
579	1-iodobutane	$-CH_2CH_2CH_2CH_3$
580	1-iodopropane	$-CH_2CH_2CH_3$
581	iodomethane	$-CH_3$

Examples 582

2-Isopropyl-1-methyl-2H-pyrazolo[3,4-c]quinolin-4-amine



Part A

A poly(tetrafluoroethylene)-lined steel pressure vessel containing a solution of 2-benzyl-1-methyl-2H-pyrazolo[3,4-c]quinolin-4-amine (prepared as described in Example 36, 0.8821 g, 3.06 mmol) in anhydrous hydrogen bromide in acetic acid (10 mL) was

heated in a 140 °C oven for 17 hours. The vessel was allowed to cool to room temperature. A solid formed that was isolated by filtration and washed with water to yield 1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine that was used in the next step.

Part B

The general method described in Part B of Examples 579-581 was used to convert the material from Part A into 2-isopropyl-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine, using 2-iodopropane as the alkyl iodide. The purification method described for Example 579 was used to provide 0.0398 g of 2-isopropyl-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white powder, mp 221.0–222.0 °C.

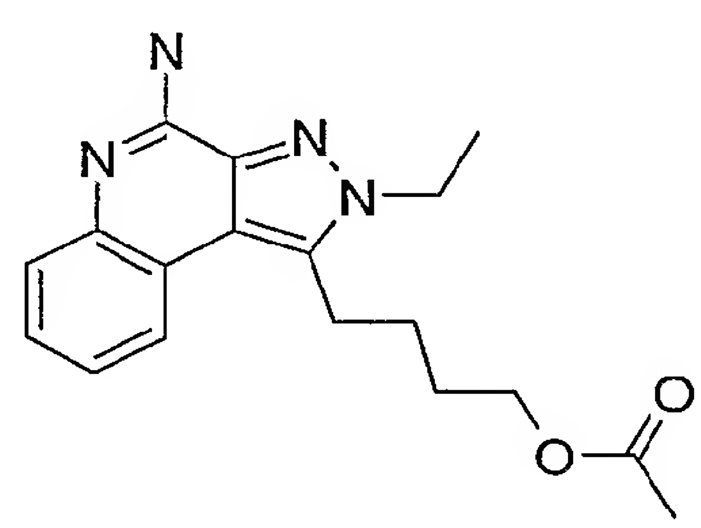
^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.02 (dd, J = 7.9, 1.2 Hz, 1H), 7.49 (dd, J = 8.1, 1.0 Hz, 1H), 7.32 (td, J = 7.1, 1.5 Hz, 1H), 7.20 (td, J = 7.9, 1.3 Hz, 1H), 6.52 (br s, 2H), 4.94 (septet, J = 6.6 Hz, 1H), 2.84 (s, 3H), 1.53 (d, J = 6.6 Hz, 6H);

MS (APCI) *m/z* 241 (M + H)$^+$;

Anal. calcd for $C_{14}H_{16}N_4 \cdot 0.15\ H_2O$: C,69.21; H, 6.76; N, 23.06. Found: C, 68.81; H, 6.60; N, 22.85.

Example 583

4-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl acetate

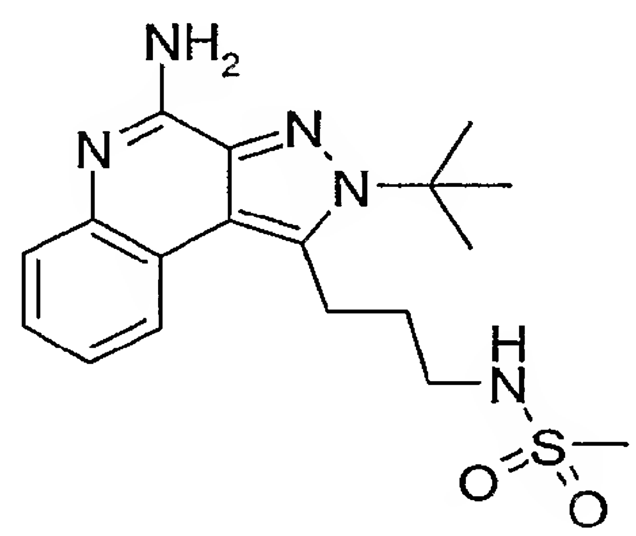


1-(4-Chlorobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (3.8 g, 12.5 mmol, prepared as described in Example 19) was combined with potassium acetate (3.68 g, 37.5 mmol), sodium iodide (470 mg, 3.12 mmol), and DMF (21 mL). The mixture was heated at 90 °C for 2 hours, allowed to cool to ambient temperature, diluted with water (100 mL), stirred for 20 minutes, and then filtered to remove a black solid. The filtrate was allowed to stand for 1 week at which time crystals had formed. The crystals were isolated by filtration, purified by chromatography on a HORIZON HPFC system (25+M cartridge eluting with chloroform/CMA in a gradient from 100:0 to 70:30), and then recrystallized

from acetonitrile to provide 55 mg of 4-(4-amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl acetate as a tan crystalline solid, mp 128-129 °C. MS (APCI) *m/z* 327 $(M + H)^+$; Anal. calcd for $C_{18}H_{22}N_4O_2$: C, 66.24; H, 6.79; N, 17.17. Found: C, 66.01; H, 6.89; N, 17.24.

Example 584

N-[3-(4-Amino-2-*tert*-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)propyl]methanesulfonamide



Part A

Under a nitrogen atmosphere, a mixture sodium *tert*-butoxide (88.45 g, 0.920 mol) and ethanol (625 mL) was stirred for 5 minutes and then cooled to 0 °C. A solution of diethyl oxalate (119 mL, 0.877 mol) and 6-chloro-2-pentanone (100 mL, 0.877 mol) in a minimal amount of ethanol was added and a precipitate formed immediately. The reaction was stirred for 5 minutes, then acetic acid (438 mL of 2 M) was added and a solution was obtained. Potassium acetate (129.0 g, 1.314 mol) was added and the reaction mixture was stirred for 3 minutes at which time it solidified. *tert*-Butylhydrazine oxalate hydrochloride (120.1 g, 0.964 mol) was added. The reaction was allowed to warm to ambient temperature with stirring overnight and then concentrated under reduced pressure. The residue was diluted with dichloromethane and water and the mixture was adjusted to pH 11 with the addition of 2 M aqueous sodium carbonate. The aqueous layer was extracted with dichloromethane; the combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 1-*tert*-butyl-5-(3-chloropropyl)-1*H*-pyrazole-3-carboxylate that was used without purification.

Part B

The material from Part A was combined with 6 M sodium hydroxide (292 mL) and ethanol (219 mL), stirred at ambient temperature for 4 hours, and then concentrated under

reduced pressure. The residue was dissolved in water. The solution was extracted with diethyl ether (2 x 100 mL) and then acidified to pH 4 with 3 N hydrochloric acid. A precipitate formed; the mixture was stirred for 30 minutes and then filtered. The isolated solid was washed with water and then air dried for 48 hours to provide 65.9 g of 1-*tert*-butyl-5-(3-chloropropyl)-1*H*-pyrazole-3-carboxylic acid as a tan solid.

Part C

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.63 g, 45.0 mmol) was added to a solution of material from Part B (10 g, 40.9 mmol) and 1-hydroxybenzotriazole hydrate (6.08 g, 45.0 mmol) in DMF (70 mL). The solution was stirred for 30 minutes and then cooled to 0 °C. Ammonium hydroxide (8.1 mL of 15 M, 123 mmol) was added and the solution was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with water (200 mL) and then extracted with diethyl ether (4 x 150 mL). The combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 1-*tert*-butyl-5-(3-chloropropyl)-1*H*-pyrazole-3-carboxamide as a brown oil.

Part D

The material from Part C, triethylamine (17.1 mL, 123 mmol), and dichloromethane (136 mL) were combined and then cooled to 0 °C. Trifluoroacetic anhydride (6.3 mL, 45 mmol) was added dropwise over a period of 1 minute. The reaction mixture was stirred for 2 hours and then quenched with saturated ammonium chloride solution (30 mL). The reaction mixture was diluted with water and then extracted with dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 1-*tert*-butyl-5-(3-chloropropyl)-1*H*-pyrazole-3-carbonitrile.

Part E

Bromine (2.5 mL, 49 mmol) was added in a single portion to a mixture of the material from Part D, potassium acetate (8.0 g, 82 mmol), and acetic acid (82 mL). The reaction mixture was stirred for 24 hours, quenched with sodium bisulfite, and then concentrated under reduced pressure. The residue was diluted with dichloromethane and water and the mixture was adjusted to pH 11 with aqueous sodium carbonate. The aqueous layer was extracted with dichloromethane. The combined organics were dried

over sodium sulfate, filtered, and then concentrated under reduced pressure to provide a black oil. The oil was purified by column chromatography (silica gel eluting with 7:3 hexanes:ethyl acetate) to provide 7.5 g of a dark yellow oil. Analysis by NMR indicated that the oil contained 4-bromo-1-*tert*-butyl-5-(3-chloropropyl)-1*H*-pyrazole-3-carbonitrile and starting material in about a 9:1 ratio.

Part F

2-Aminophenylboronic acid hydrochloride (8.5 g, 49.2 mmol), potassium phosphate (15.6 g, 73.8 mmol), tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (563 mg, 0.615 mmol), and bis[(2-diphenylphosphino)phenyl]ether (397 mg, 0.738 mmol) were added to a solution of the material from Part E in toluene (153 mL) containing powdered molecular sieves (1 g). Nitrogen was bubbled through the reaction mixture, and then the reaction was heated at 110 °C for 24 hours. The mixture was cooled to ambient temperature and then filtered through a layer of silica gel (eluting with 3:2 chloroform/methanol). The filtrate was concentrated under reduced pressure and the residue was dissolved in ethanol (120 mL). Hydrogen chloride (20 mL of a 4 M solution in ethanol) was added to the resulting solution, and the reaction was heated at reflux for two hours and then allowed to cool to ambient temperature. The solvent was removed under reduced pressure and the residue was adjusted to pH 10 with the addition of 2 M aqueous sodium carbonate. The mixture was diluted with brine and extracted with dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (65+M cartridge, eluting with chloroform/CMA in a gradient from 100:0 to 70:30). The cleanest fractions were combined and concentrated under reduced pressure. The residue was recrystallized from acetonitrile to provide 250 mg of off white crystals. The remaining fractions and the mother liquor from the recrystallization were combined and concentrated to provide 2 g of 2-*tert*-butyl-1-(3-chloropropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a yellow solid.

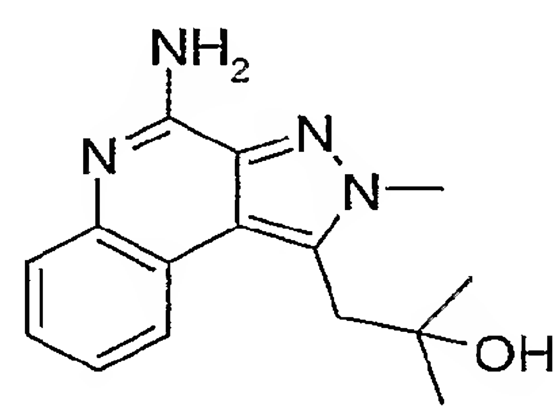
Part G

Methanesulfonamide (3.0 g, 31.5 mmol) was added to a chilled (0 °C) suspension of sodium hydride (60% dispersion in mineral oil, 1.2 g, 31.5 mmol) in DMF (10 mL); the reaction was stirred at ambient temperature for five minutes. The yellow solid from Part

F, DMF (4 mL) and sodium iodide (235 mg, 1.57 mmol) were sequentially added. The reaction was heated at 90 °C for three hours, allowed to cool to ambient temperature, and then poured into ice water (100 mL). The mixture was stirred at ambient temperature for 1 hour at which time a precipitate formed. The solid was isolated by filtration and then dissolved in a mixture of dichloromethane and chloroform. The solution was dried over sodium sulfate and then purified by chromatography on a HORIZON HPFC system (40+M cartridge eluting with chloroform/CMA in a gradient from 100:0 to 70:30). The resulting solid was recrystallized from acetonitrile to provide 80 mg of *N*-[3-(4-amino-2-*tert*-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)propyl]methanesulfonamide as gray crystals, mp 223-224 °C. MS (APCI) *m/z* 376 $(M + H)^+$; Anal. calcd for $C_{18}H_{25}N_5O_2S$: C, 57.58; H, 6.71; N, 18.65 Found: C, 57.71; H, 7.00; N, 18.81.

Example 585

1-(4-Amino-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol



Part A

Under a nitrogen atmosphere, sodium *tert*-butoxide (54.1 g, 0.564 mol) and ethanol (187 mL) were combined at 0 °C. The mixture was stirred at ambient temperature for 30 minutes. A mixture of mesityl oxide (30 mL, 0.26 mol) and diethyl oxalate (35.6 mL, 0.26 mol) in ethanol (40 mL) was added over a period of 1 minute. The reaction mixture was stirred for 2.5 hours at ambient temperature and then cooled to 0 °C. Acetic acid (131 mL) and methyl hydrazine (15.3 mL, 0.288 mol) were added. The reaction was allowed to warm to ambient temperature with stirring overnight and then concentrated under reduced pressure. The residue was diluted with chloroform (500 mL) and water (1 L) and the mixture was adjusted to pH 11 with the addition of 50% sodium hydroxide. The aqueous layer was extracted with chloroform (3 x 250 mL); the combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide ethyl 1-

methyl-5-(2-methylprop-1-enyl)-1*H*-pyrazole-3-carboxylate as a black oil that was used without purification.

Part B

The material from Part B was combined with 6 M sodium hydroxide (87 mL) and ethanol (655 mL), stirred at ambient temperature for 2 hours, and then concentrated under reduced pressure. The residue was dissolved in water and the solution acidified to pH 4 by the addition of 3 N hydrochloric acid. A precipitate formed; the mixture was stirred for 30 minutes and then filtered. The isolated solid was washed with water and then air dried for 24 hours to provide 39 g of 1-methyl-5-(2-methylprop-1-enyl)-1*H*-pyrazole-3-carboxylic acid as a tan solid.

Part C

The material from Part B was combined with dichloromethane (870 mL) and a drop of DMF. Oxalyl chloride (45.8 mL, 525 mmol) was added. The reaction mixture was stirred at ambient temperature for 30 minutes and then cooled to 0 °C. Chilled (0 °C) ammonium hydroxide (250 mL of 15 M) was added in a single portion. The reaction mixture was stirred for 1 hour and then extracted with chloroform. The combined extracts were dried and then concentrated under reduced pressure to provide 31.9 g of 1-methyl-5-(2-methylprop-1-enyl)-1*H*-pyrazole-3-carboxamide as a brown oil.

Part D

The material from Part C was combined with toluene (250 mL) and stirred until a solution was obtained. Phosphorous oxychloride (28.5 mL, 302 mmol) was added and the reaction mixture was heated at reflux for 4 hours. The toluene layer was poured into ice water; the mixture was made basic by the addition of 2 N aqueous sodium carbonate and then extracted with chloroform. The extracts were dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 1-methyl-5-(2-methylprop-1-enyl)-1*H*-pyrazole-3-carbonitrile as a dark oil.

Part E

mCPBA (57 g of 50%) was added in a single portion to a solution of the material from Part D in dichloromethane (750 mL). The reaction mixture was stirred at ambient temperature overnight and then filtered to remove the chlorobenzoic acid. The filter cake was rinsed with a small amount of dichloromethane. The filtrate was washed with

aqueous saturated sodium bicarbonate. The aqueous layer was extracted with dichloromethane (1 x 200 mL). The combined organics were dried over sodium sulfate, filtered, and then concentrated under reduced pressure to provide 5-(3,3-dimethyloxiran-2-yl)-1-methyl-1*H*-pyrazole-3-carbonitrile.

Part F

Bromine (16.14 mL, 315 mmol) was added to a solution of the material from Part E in acetic acid (300 mL) at 0 °C. The red solution was stirred at ambient temperature for 2 hours, and then saturated aqueous sodium bisulfite was added until the red color was gone. The mixture was concentrated under reduced pressure to remove the acetic acid. The residue was diluted with chloroform (100 mL) and the pH was adjusted with 2 M aqueous sodium carbonate to pH 11. The cloudy mixture was diluted with water (50 mL) and extracted with chloroform (3 x 75 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to a cloudy oil. The oil was combined with acetonitrile (300 mL) and aqueous hydrogen bromide (35 mL of 48%) and stirred for 1 hour. Aqueous saturated sodium bicarbonate was added until the mixture was basic. The resulting solution was diluted with water and then extracted with dichloromethane. The extracts were dried and concentrated under reduced pressure to provide a dark yellow oil. The oil was purified by chromatography on a HORIZON HPFC system (eluting with hexanes/ethyl acetate in a gradient from 9:1 to 1:1) to provide 10.5 g of crude 4-bromo-5-(1-bromo-2-hydroxy-2-methylpropyl)-1-methyl-1*H*-pyrazole-3-carbonitrile.

Part G

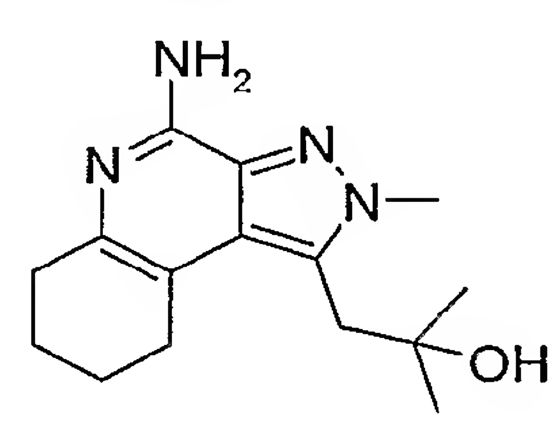
Azobisisobutyronitrile (600 mg, 3.6 mmol) and tributyltin hydride (7.3 mL, 27.3 mmol) were added to a mixture of portion of the material from Part E (6.4 g, 18 mmol) and toluene (91 mL). After bubbling had ceased, the pale yellow solution was heated at 90 °C for 1 hour. Analysis by TLC indicated that starting material was still present. An additional equivalent of tributyltin hydride was added and the reaction mixture was heated for an additional 30 minutes; this was repeated. The reaction mixture was purified by chromatography on a HORIZON HPFC system (65+M cartridge eluting with hexanes/ethyl acetate in a gradient from all hexane to 1:1) to provide 2.7 g of 4-bromo-5-(2-hydroxy-2-methylpropyl)-1-methyl-1*H*-pyrazole-3-carbonitrile as a colorless oil.

Part H

2-Aminophenylboronic acid hydrochloride (3.6 g, 20.8 mmol), potassium phosphate (11.0 g, 52.0 mmol), tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (238 mg, 0.26 mmol), and bis[(2-diphenylphosphino)phenyl]ether (167 mg, 0.312 mmol) were added to a solution of the material from Part G in toluene (65 mL) containing powdered molecular sieves (1 g). Nitrogen was bubbled through the reaction mixture, and then the reaction was heated at 110 °C for 24 hours. The mixture was cooled to ambient temperature and then filtered through a layer of silica gel (eluting with 3:2 chloroform/methanol). The filtrate was concentrated under reduced pressure and dissolved in ethanol (52 mL). Hydrogen chloride (4.8 mL of a 4 M solution in ethanol) was added to the resulting solution, and the reaction was heated at reflux for two hours and allowed to cool to ambient temperature. The solvent was removed under reduced pressure and the residue was adjusted to pH 10 with the addition of 2 M aqueous sodium carbonate. The mixture was diluted with brine and chloroform. A white solid that did not dissolve in either layer was isolated by filtration and then recrystallized from ethanol to provide 300 mg of 1-(4-amino-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol as gray crystals, mp 256-257 °C. MS (APCI) *m/z* 271 $(M + H)^+$; Anal. calcd for $C_{15}H_{18}N_4O$: C, 66.65; H, 6.71; N, 20.73. Found: C, 66.51; H, 6.89; N, 20.79.

Example 586

1-(4-Amino-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol

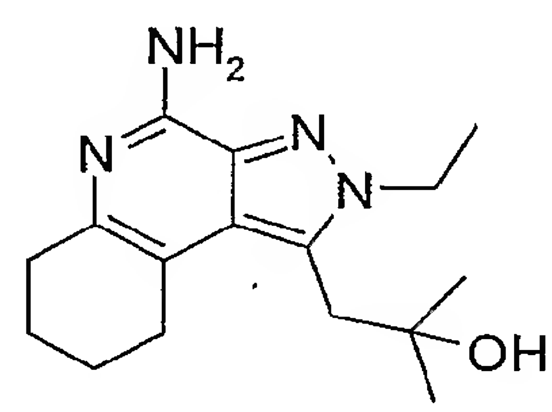


The mother liquor from Example 585 Part H was concentrated to provide 1 g of 1-(4-amino-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol. This material was combined with platinum oxide (750 mg) and trifluoroacetic acid (25 mL) and shaken under hydrogen pressure on a Parr apparatus for 2 days. The reaction mixture was filtered

through a layer of CELITE filter agent and the filter cake was rinsed with dichloromethane. The filtrate was concentrated under reduced pressure. The residue was diluted with water (10 mL), the pH was adjusted to pH 12 with 50% sodium hydroxide, and the mixture was extracted with dichloromethane. The extracts were dried over sodium sulfate and then purified by chromatography on a HORIZON HPFC system (40+M cartridge eluting with a gradient of 0 to 30 % CMA in chloroform). The resulting solid was recrystallized from acetonitrile to provide 160 mg of 1-(4-amino-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol as tan crystals, mp 228-234 °C. MS (APCI) *m/z* 275 $(M + H)^+$; Anal. calcd for $C_{15}H_{22}N_4O$: C, 65.67; H, 8.08; N, 20.42. Found: C, 65.53; H, 8.19; N, 20.47.

Example 587

1-(4-Amino-2-ethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol

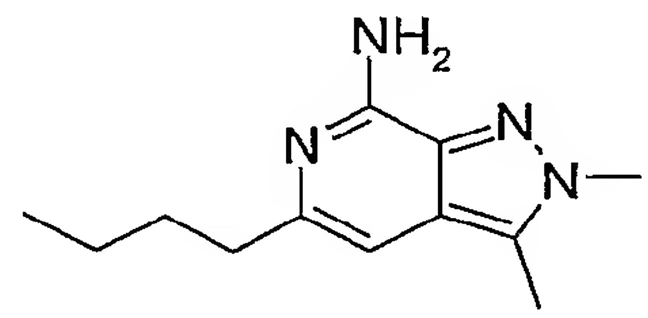


Using the method of Example 586, 1-(4-amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol (100 mg, prepared as described in Example 62) was reduced and purified to provide 25 mg of 1-(4-amino-2-ethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-2-methylpropan-2-ol as a white powder, mp 202-204 °C. ^1H NMR (500 MHz, DMSO-d_6) δ 5.96 (s, 2H), 4.55 (s, 1H), 4.46 (q, J = 7.2 Hz, 2H), 3.12 (s, 2H), 2.82 (m, 2H), 2.57 (m, 2H), 1.72 (m, 4H), 1.39 (t, J = 7.2 Hz, 3H), 1.34 (s, 6H); ^{13}C NMR (75 MHz, DMSO-d_6)

δ 149.11, 141.0, 135.20, 132.16, 123.77, 110.30, 70.70, 45.56, 37.93, 32.09, 30.18, 25.10, 23.46, 23.15, 15.91;MS (APCI) *m/z* 289 $(M + H)^+$; Anal. calcd for $C_{16}H_{24}N_4O$: C, 66.64; H, 8.39; N, 19.43. Found: C, 66.46; H, 8.58; N, 19.23.

Example 588

5-Butyl-2,3-dimethyl-2*H*-pyrazolo[3,4-*c*]pyridin-7-amine



Part A

Methylhydrazine (6.2 mL, 117 mmol) was added to a chilled (0 °C) solution of methyl pyruvic acetate (15.0 mL, 107 mmol) in acetic acid (210 mL). The reaction mixture was stirred for 1 hour and then concentrated under reduced pressure. The residue was diluted with water, made basic (pH 11) by the addition of aqueous saturated sodium carbonate, and then extracted with dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 14.6 g of ethyl 1,5-dimethyl-1*H*-pyrazole-3-carboxylate as a dark oil.

Part B

The material from Part A (3.0 g, 17.8 mmol) was combined in a stainless steel reactor with 7 N ammonia in methanol (30 mL). The reaction was sealed and heated at 150 °C for 24 hours. The reaction mixture was concentrated under reduced pressure to provide 2.5 g of crude 1,5-dimethyl-1*H*-pyrazole-3-carboxamide as a dark brown solid.

Part C

The material from Part B, triethylamine (7.5 mL, 54 mmol), and dichloromethane (60 mL) were combined and then cooled to 0 °C. Trifluoroacetic anhydride (3.8 mL, 27 mmol) was added dropwise over a period of 1 minute. The reaction mixture was stirred for 2 hours and then quenched with saturated ammonium chloride solution (30 mL). The reaction mixture was diluted with water and then extracted with dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with a gradient of 0 to 50% ethyl acetate in hexanes) to provide 1,5-dimethyl-1*H*-pyrazole-3-carbonitrile as a white solid.

Part D

A solution of iodine monochloride (3.9 g, 24.6 mmol) in dichloromethane (12 mL) was added to a mixture of material from Part C (1.5 g, 12.3 mmol), dichloromethane (20 mL) and freshly ground potassium carbonate (3.2 g, 23 mmol). After 1 hour the reaction mixture was quenched with sodium bisulfite until all color was gone, diluted with water, and then extracted with dichloromethane. The combined extracts were dried over sodium sulfate, filtered, and then concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with a gradient of 0 to 50% ethyl acetate in hexanes) to provide 2.5 g of 4-iodo-1,5-dimethyl-1*H*-pyrazole-3-carbonitrile as a white solid.

Part E

Under a nitrogen atmosphere, material from Part D (200 mg, 0.81 mmol), hexyne (0.18 mL, 1.6 mmol), copper(I) iodide (30 mg, 0.16 mmol), dichlorobis(triphenylphosphine)palladium(II) (57 mg, 0.081 mmol), triethylamine (0.24 mL, 2.4 mmol) and acetonitrile (4 mL) were combined and then heated at reflux for 1 hour. The reaction mixture was cooled to ambient temperature, diluted with 7:3 hexanes:ethyl acetate, and then filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure. The residue was purified by chromatography on a HORIZON HPFC system (25+M cartridge, eluting with a gradient of 0 to 50% ethyl acetate in hexanes) to provide 140 mg of 4-(hex-1-ynyl)-1,5-dimethyl-1*H*-pyrazole-3-carbonitrile as a brown oil.

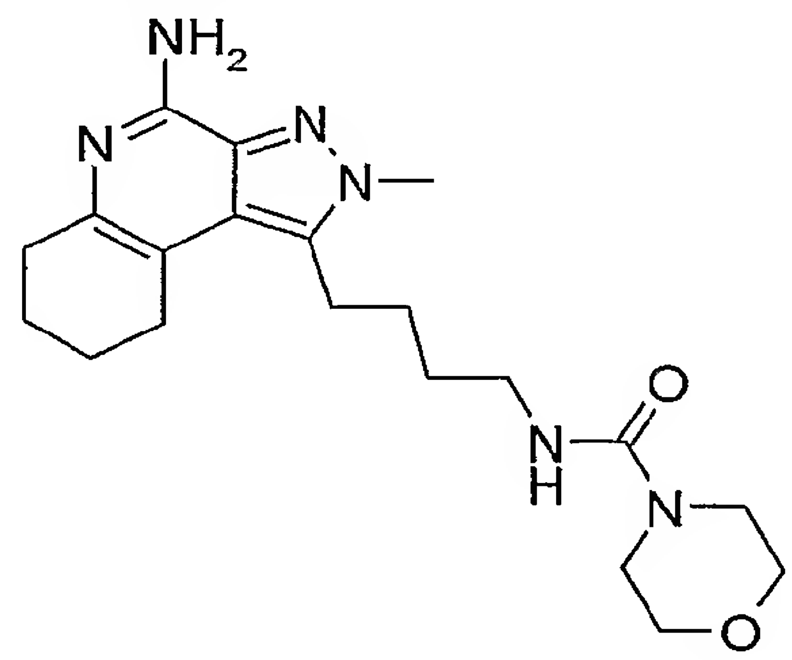
Part F

The material from Part E was combined in a stainless steel reactor with 7 N ammonia in methanol (10 mL). The reaction was sealed and heated at 150 °C for 58 hours. The reaction mixture was concentrated under reduced pressure to provide a brown oil. The oil was purified by chromatography on a HORIZON HPFC system (40+M cartridge, eluting with a gradient of 0 to 20% CMA in chloroform) to provide a tan solid. This material was triturated with acetonitrile to provide 60 mg of 5-butyl-2,3-dimethyl-2*H*-pyrazolo[3,4-*c*]pyridin-7-amine as a tan powder, mp 130-131 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.45 (s, 1H), 6.17 (s, 2H), 4.00 (s, 3H), 2.46-2.49 (m, 5H), 1.16 (m, 2H), 1.30 (m, 2H), 0.89 (t, J = 7.25 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 149.15,146.42,

133.04, 129.13, 122.17, 97.71, 36.10, 36.05, 30.44, 20.79, 12.80, 8.39;MS (APCI) *m/z* 219.2 $(M + H)^+$; HRMS (ESI) calcd for $C_{12}H_{18}N_4 + H$: 219.161, found 219.1594. Anal. calcd for $C_{12}H_{18}N_4$•0.15 H_2O: C, 65.22; H, 8.35; N, 25.35. Found: C, 65.52; H, 8.72; N, 25.64.

Example 589

N-[4-(4-Amino-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]morpholine-4-carboxamide



Part A

A mixture of 1-(4-chlorobutyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine (2.8 g, 8.6 mmol, prepared as described in Part F of Examples 454-488), platinum oxide, and trifluoroacetic acid was shaken under hydrogen pressure on a Parr apparatus for 2 days. The reaction mixture was filtered through a layer of CELITE filter agent and the filter cake was rinsed with methanol. The filtrate was concentrated under reduced pressure. The residue was diluted with water (10 mL), the pH was adjusted to pH 12 with 50% sodium hydroxide, and the mixture was extracted with dichloromethane. The extracts were dried over sodium sulfate and concentrated under reduce pressure. The residue was purified by chromatography on a HORIZON HPFC system (40+M cartridge eluting with a gradient of 0 to 20 % CMA in chloroform) to provide 2.0 g of 1-(4-chlorobutyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine as a yellow solid.

Part B

A mixture of 1-(4-chlorobutyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine (385 mg, 1.31 mmol), potassium phthalimide (362 mg, 1.96 mmol),

sodium iodide (50 mg, 0.327 mmol), and DMF (2 mL) was heated at 90 °C for 4 hours. The reaction mixture was cooled to ambient temperature and then diluted with water (30 mL) while stirring in an ice bath. A precipitate was isolated by filtration to obtain 2-[4-(4-amino-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]-1*H*-isoindole-1,3(2*H*)-dione as a yellow solid.

Part C

The material from Part B was combined with hydrazine hydrate (0.3 mL, 6.55 mmol) and ethanol (15 mL) and heated at reflux for 30 minutes. The reaction mixture was chilled to 0 °C. A precipitate was removed by filtration and the filter cake was rinsed with ethanol. The filtrate was purified by chromatography on a HORIZON HPFC system (25+M cartridge eluting with a gradient of 0 to 40 % CMA in chloroform) to provide 290 mg of 1-(4-aminobutyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine.

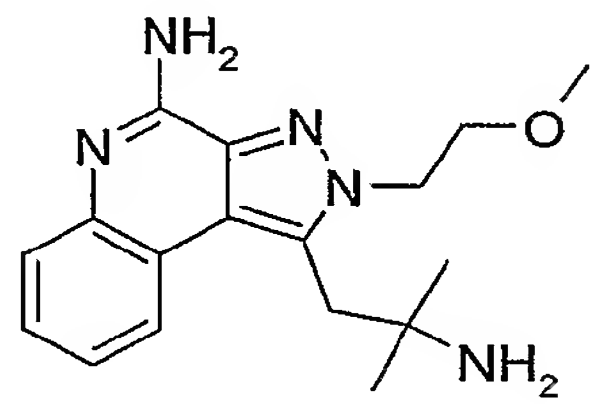
Part D

Under a nitrogen atmosphere, a mixture of the material from Part C, triethylamine (290 μL, 2.12 mmol), and dichloromethane (5 mL) was cooled to 0 °C. 4-Morpholinecarbonyl chloride (124 μL, 1.06 mmol) was added in 3 portions spaced 5 minutes apart. The reaction mixture was warmed to ambient temperature and stirred for 1 hour. The reaction mixture was quenched with saturated aqueous ammonium chloride, diluted with water, and then extracted with chloroform. The extract was dried over sodium sulfate, filtered, and then purified by chromatography on a HORIZON HPFC system (25+M cartridge eluting with a gradient of 0 to 20 % CMA in chloroform) to provide a clear oil. The oil was dissolved in acetonitrile. The acetonitrile was removed under reduced pressure and the residue was placed under high vacuum with gentle heating to provide *N*-[4-(4-amino-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butyl]morpholine-4-carboxamide as a white powder, mp 95 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.48 (t, J = 5.3 Hz, 1H), 5.99 (s, 2H), 4.00 (s, 3H), 3.51 (t, J = 4.5 Hz, 4H), 3.22 (t, J = 5.0 Hz, 4H), 3.07 (q, J = 5.6 Hz, 2H), 3.00 (t, J = 7.3 Hz, 2H), 2.80 (bs, 2H), 2.56 (bs, 2H), 1.74 (m, 4H) 1.51 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.51, 147.42, 139.56, 134.11, 133.45, 120.94, 108.33, 64.81, 42.72, 39.56, 36.15, 30.41, 28.38,

26.42, 23.40, 23.23, 21.90, 21.57; MS (APCI) *m/z* 387 $(M + H)^+$; Anal. calcd for $C_{20}H_{30}N_6O_2 \bullet H_2O$: C, 59.39; H, 7.97; N, 20.78. Found: C, 59.04; H, 7.89; N, 20.74.

Example 590

1-(2-Amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Under a nitrogen atmosphere, 2-bromoethyl methyl ether (19.7 g, 142 mmol) was added to a mixture of ethyl 5-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl}-1*H*-pyrazole-3-carboxylate (40 g, 129 mmol, prepared according to the method of Example 64 Part A using hydrazine hydrate in lieu of propylhydrazine oxalate) and sodium *tert*-butoxide (12.4 g, 129 mmol) in ethanol (128 mL). The reaction mixture was heated at reflux for 5 hours; an additional 0.2 equivalents of both sodium *tert*-butoxide and 2-bromoethyl methyl ether were added, and the reaction mixture was heated at reflux for an additional 21 hours. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between water and *tert*-butyl methyl ether. The aqueous layer was extracted with *tert*-butyl methyl ether (x 3). The combined organics were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 46.0 g of a yellow oil. The oil was dissolved in 1:1 *tert*-butyl methyl ether:hexanes and purified by IFC (65 cartridge eluting with 1:1 *tert*-butyl methyl ether:hexanes) to provide a pale yellow oil. This material was triturated with 40 mL of 1:1 *tert*-butyl methyl ether:hexanes, seeded with product from an earlier run, stirred until a white solid formed, and then concentrated under reduced pressure to provide 24.83 g of ethyl 5-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl}-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylate as a white solid, mp 92-93 °C. MS (APCI) m/z 370 $(M + H)^+$; Anal. Cacld for $C_{18}H_{31}N_3O_5$: C, 58.52; H, 8.46; N, 11.37. Found: C, 58.65; H, 8.69; N, 11.47.

Part B

Lithium hydroxide (17.1 g, 407 mmol) was added to a solution of ethyl 5-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl}-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylate (37.6 g, 102 mmol) in methanol (141 mL) and water (47 mL). The reaction mixture was stirred for 2 days and then most of the methanol was removed under reduced pressure. The aqueous residue was cooled in an ice bath and then combined with 1 N hydrochloric acid (350 mL) and *tert*-butyl methyl ether. The layers were separated. The volume of the organic layer was reduced under vacuum and then diluted with hexanes. A precipitate was isolated by filtration, washed with water, and suction dried to provide 13.09 g of 5-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl}-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylic acid as a white solid. The aqueous layer was extracted with chloroform while maintaining the pH of the aqueous layer at pH 4-5 by the addition of 1 N hydrochloric acid. The chloroform extracts were combined, dried over sodium sulfate and magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dissolved in *tert*-butyl methyl ether, diluted with hexanes, and then concentrated under reduced pressure. A white solid was isolated by filtration, washed with hexanes, and suction dried to provide an additional 21.8 g of product.

Part C

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (21.5 g, 112 mmol) was added to a solution of 5-{2-[(*tert*-butoxycarbonyl)amino]-2-methylpropyl}-1-(2-methoxyethyl)-1*H*-pyrazole-3-carboxylic acid (34.8 g, 102 mmol) and 1-hydroxybenzotriazole (15.2 g, 112 mmol) in DMF (174 mL) at ambient temperature. The mixture was stirred for 2.5 hours until a solution formed and then it was cooled in an ice bath. Concentrated ammonium hydroxide (20.4 mL) was added and the reaction mixture was stirred for 30 minutes. Water (445 mL) was added and the mixture was extracted with *tert*-butyl methyl ether (x 12). The extracts were combined, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was concentrated twice from xylene under reduced pressure to provide 38 g of an oil. The oil was combined with 100 mL of 1:1 *tert*-butyl methyl ether:hexanes, warmed until a solution was obtained, and then let stand. An oil formed; the mixture was concentrated under reduced pressure. The residue was dried under vacuum at 50 °C until a solid formed. The solid was slurried with

hexanes, isolated by filtration, washed with hexanes, and suction dried to provide 31.3 g of *tert*-butyl 2-[3-(aminocarbonyl)-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl]-1,1-dimethylethylcarbamate as a white solid.

Part D

Using the method of Example 64 Part D, *tert*-butyl 2-[3-(aminocarbonyl)-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl]-1,1-dimethylethylcarbamate (31.1 g) was dehydrated. The crude product was purified by IFC (65+M cartridge eluting with a gradient of 50 to 60% ethyl acetate in hexanes) to provide 28.12 g of *tert*-butyl 2-[3-cyano-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl]-1,1-dimethylethylcarbamate as a white solid.

Part E

Bromine (19.5 g, 122 mmol) was added in a single portion to a solution of *tert*-butyl 2-[3-cyano-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl]-1,1-dimethylethylcarbamate (28.07 g, 87.1 mmol) and potassium acetate (12.8 g, 131 mmol) in acetic acid (174.2 mL). After 16 hours saturated aqueous sodium bisulfite was added until the reaction mixture was colorless. The acetic acid was removed under reduced pressure at about 30 °C. The residue was made basic with 2 M sodium carbonate and then extracted with *tert*-butyl methyl ether (x 3). The extracts were combined, dried over magnesium sulfate, and concentrated under reduced pressure. Analysis by HPLC indicated that the BOC group had been partially removed. The material was dissolved in dichloromethane (50 mL), combined with di-*tert*-butyl dicarbonate, and stirred for 9 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by IFC (65+M cartridge eluting with a gradient of 40 to 50% *tert*-butyl methyl ether in hexanes) to provide 32.1 g of *tert*-butyl 2-[4-bromo-3-cyano-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl]-1,1-dimethylethylcarbamate as a colorless, viscous resin.

Part F

Using the method of Example 64 Part F, *tert*-butyl 2-[4-bromo-3-cyano-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl]-1,1-dimethylethylcarbamate (32.1 g, 80.0 mmol) was coupled with 2-aminophenylboronic acid. The reaction mixture was partitioned between water and *tert*-butyl methyl ether. The aqueous layer was extracted with *tert*-butyl methyl ether (x2). The combined extracts were dried over magnesium sulfate, filtered, and concentrated to provide a brown oil. The oil was purified by chromatography on a

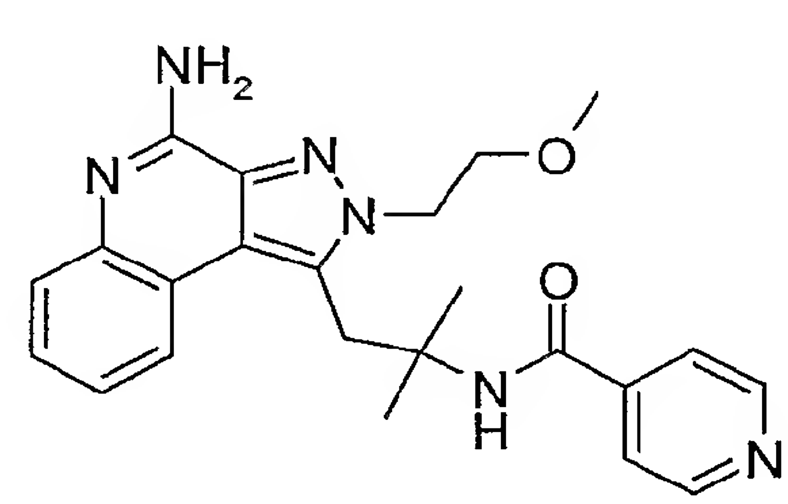
HORIZON HPFC system (65+M cartridge eluting with a gradient of 1 to 20% CMA in chloroform) to provide 11.4 g of an orange resin. This material was purified IFC (65+M cartridge eluting with a gradient of 35 to 55% ethyl acetate in hexanes) to provide 4.85 g of *tert*-butyl 2-[4-(2-aminophenyl)-3-cyano-1-(2-methoxyethyl)-1*H*-pyrazol-5-yl]-1,1-dimethylethylcarbamate as an orange glassy resin.

Part G

Under a nitrogen atmosphere, acetyl chloride (100 mmol) was added to ice cold ethanol (100 mL). The ice bath was removed; the mixture was stirred for 3 hours and then combined with the material from Part F. The reaction mixture was heated at reflux for 2 hours and then concentrated under reduced pressure. The residue was combined with 2 M aqueous sodium carbonate (50 mL) and then extracted with chloroform (x 4). The combined extracts were dried over sodium sulfate, filtered, and concentrated to provide 3.84 g of an orange solid. This material was purified by IFC (40+M cartridge eluting with a gradient of 25 to 55% CMA in chloroform) to provide 2.15 g of a white solid. This material was refluxed with 3:1 ethyl acetate: hexanes (100 mL), chilled in an ice bath, isolated by filtration, rinsed with a small amount of the solvent mixture, and then suction dried to provide 1.94 g of a white solid. A portion (165 mg) of this material was recrystallized from acetonitrile (10 mL) to provide 109 mg of 1-(2-amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white solid, mp 199-200 °C. MS (APCI) m/z 314 $(M + H)^+$; Anal. Calcd for $C_{17}H_{23}N_5O$: C, 65.15; H, 7.40; N, 22.35. Found: C, 64.83; H, 7.38; N, 22.70.

Example 591

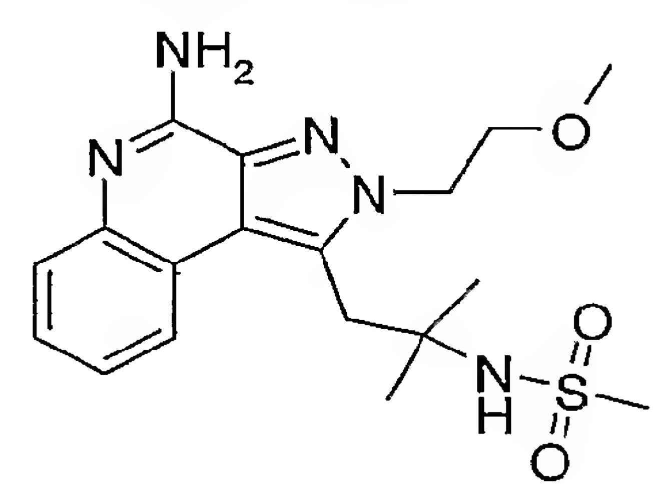
N-{2-[4-Amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}isonicotinamide



Using the method of Example 68, isonicotinoyl chloride hydrochloride (710 mg, 4.00 mmol) was reacted with 1-(2-amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (500 mg, 1.60 mmol, prepared as described in Example 590). The crude product was purified as described in Example 68 to provide 551 mg of *N*-{2-[4-amino-2-(methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}isonicotinamide as a white solid, mp 166-168 °C. MS (ESI) m/z 419 (M + H)$^+$; Anal. Calcd for $C_{23}H_{26}N_6O_2$: C, 66.01; H, 6.26; N, 20.08. Found: C, 65.93; H, 6.41; N, 20.44.

Example 592

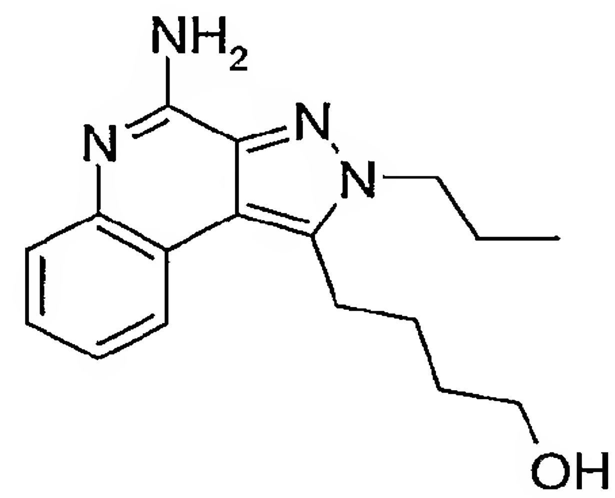
N-{2-[4-Amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide



Using the method of Example 66, methanesulfonyl chloride (399 mg, 3.48 mmol) was reacted with 1-(2-amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (1.09 g, 3.48 mmol, prepared as described in Example 590). The crude product was purified by IFC (40M cartridge eluting with a gradient of 15 to 35 % CMA in chloroform) to provide a white foam. The foam was refluxed with 35% ethyl acetate in hexanes (50 mL), ethyl acetate was added until a free flowing white solid appeared, and then the mixture was cooled on ice. The solid was isolated by filtration and dried to provide 809 mg of *N*-{2-[4-amino-2-(methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide as a white solid, mp 211-213 °C. MS (ESI) m/z 392 (M + H)$^+$; Anal. Calcd for $C_{18}H_{25}N_5O_3S$: C, 55.22; H, 6.44; N, 17.89. Found: C, 55.05; H, 6.38; N, 17.98.

Example 593

4-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butan-1-ol



A solution of di(*tert*-butyl) 1-(4-hydroxybutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (prepared as described in Parts A-C of Example 57, 0.507 g, 1.02 mmol) in 6 M HCl in ethanol (5 mL) was heated at 60 °C for 1.5 hours. The solution was allowed to cool to room temperature, and then was concentrated under reduced pressure to yield an oil. The oil was triturated with ether to obtain a solid that was isolated by filtration. The solid was dissolved in methanol and the solution was adjusted to approximately pH 14 with 50% aqueous sodium hydroxide. The solution was concentrated under reduced pressure and the crude product was purified by chromatography (silica gel, elution with 5% CMA in chloroform) followed by crystallization from hexanes/ethyl acetate to provide 0.084 g of 4-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butan-1-ol as white needles, mp 135.0-136.0 °C.

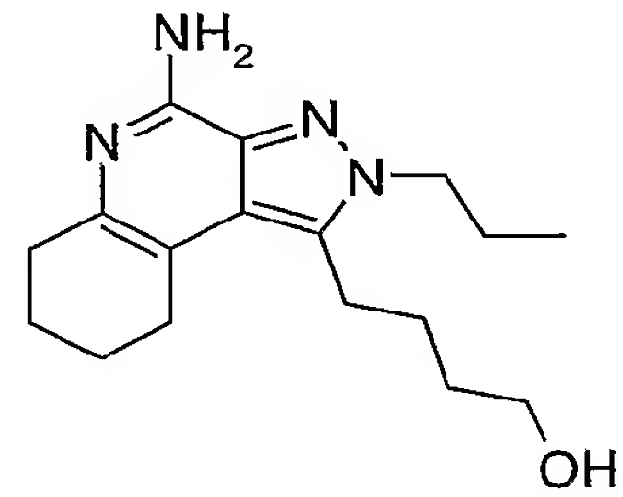
^{1}H NMR (300 MHz, DMSO) δ 7.92 (d, J = 7.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 7.0 Hz, 1H), 7.20 (t, J = 7.0 Hz, 1H), 6.64 (s, 2H), 4.43 (t, J = 5.0 Hz, 1H), 4.34 (t, J = 7.2 Hz, 2H), 3.47 (q, J = 5.8 Hz, 2H), 3.25 (t, J = 7.5 Hz, 2H), 1.85-1.99 (m, 2H), 1.70-1.77 (m, 2H), 1.56-1.66 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H);

MS (APCI) *m/z* 299 $(M + H)^+$;

Anal. calcd for $C_{17}H_{22}N_4O$: C, 68.43; H, 7.43; N, 18.78. Found: C, 68.47; H, 7.62; N, 18.84.

Example 594

4-(4-Amino-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butan-1-ol



4-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butan-1-ol (prepared as described in Example 593, 0.118 g, 0.396 mmol) was hydrogenated for 1.8 days using the method described in Example 59. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to yield an oil that was dissolved in 6 M aqueous sodium hydroxide (20 mL). The mixture was stirred for 1 day, then a white solid was isolated by filtration, washed with water, and dried at 70 °C under vacuum to provide 0.719 g of 4-(4-amino-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)butan-1-ol as a white powder, mp 194.0-200.0 °C.

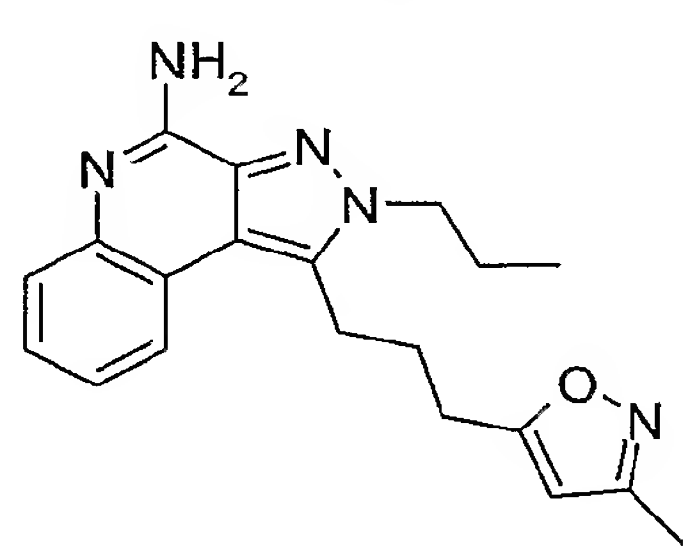
^{1}H NMR (300 MHz, DMSO) δ 5.95 (s, 2H), 4.41 (t, J = 4.7 Hz, 1H), 4.22 (t, J = 7.2 Hz, 2H), 3.44 (m, 2H), 3.00 (t, J = 7.5 Hz, 2H), 2.82 (s, 2H), 2.57 (s, 2H), 1.82-1.91 (m, 2H), 1.74 (s, 4H), 1.49-1.59 (m, 4H), 0.89 (t, J = 7.4 Hz, 3H);

MS (APCI) m/z 303 $(M + H)^+$;

Anal. calcd for $C_{17}H_{26}N_4O{\cdot}0.2\ H_2O{\cdot}0.3\ C_2F_3HO_2$: C, 62.13; H, 7.91; N, 16.47. Found: C, 62.10; H, 7.75; N, 16.40.

Example 595

1-[3-(3-Methylisoxazol-5-yl)propyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A solution of acetaldoxime (1.00 g, 16.9 mmol) and N-chlorosuccinimide (2.26 g, 16.9 mmol) in DMF (50 mL) was heated at 50 °C for 1.5 hours. The solution was allowed to cool to room temperature and was partitioned between water and ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to yield 1.0545 g of α-chloroacetaldoxime as a clear colorless oil that was used directly in the next step.

Part B

The oil from Part A (0.14 g, 1.5 mmol) was added to a solution of di(*tert*-butyl) 1-pent-4-ynyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (prepared as described in Parts A-E of Example 57, 0.590 g, 1.20 mmol) and triethylamine (0.25 mL, 1.8 mmol) in dichloromethane (10 mL). The solution was heated at 40 °C for 42 hours, during which time more of the material from Part A (0.357 g) was added. The solution was allowed to cool to room temperature, and then was diluted with dichloromethane. The solution was washed with an aqueous potassium carbonate solution, water, and brine, then was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, eluted with 40% ethyl acetate in hexanes) to provide 0.4705 g of di(*tert*-butyl) 1-[3-(3-methylisoxazol-5-yl)propyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as a colorless oil.

Part C

A solution of di(*tert*-butyl) 1-[3-(3-methylisoxazol-5-yl)propyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (0.471 g, 0.856 mmol) in 6 M HCl in ethanol (5 mL) was heated at 60 °C for 1 hour. The solution was allowed to cool to room temperature, then was concentrated under reduced pressure to yield an oil that was dissolved in water (20 mL). The solution was adjusted to pH 12 with a few drops of 50% aqueous potassium hydroxide and then to pH 14 with 1 M aqueous potassium hydroxide. A precipitate formed that was isolated by filtration and crystallized from ethyl acetate/hexanes. The crystals were isolated by filtration and dried under vacuum at 70 °C to afford 0.123 g 1-[3-(3-methylisoxazol-5-yl)propyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as white needles, mp 183.0-184.0 °C.

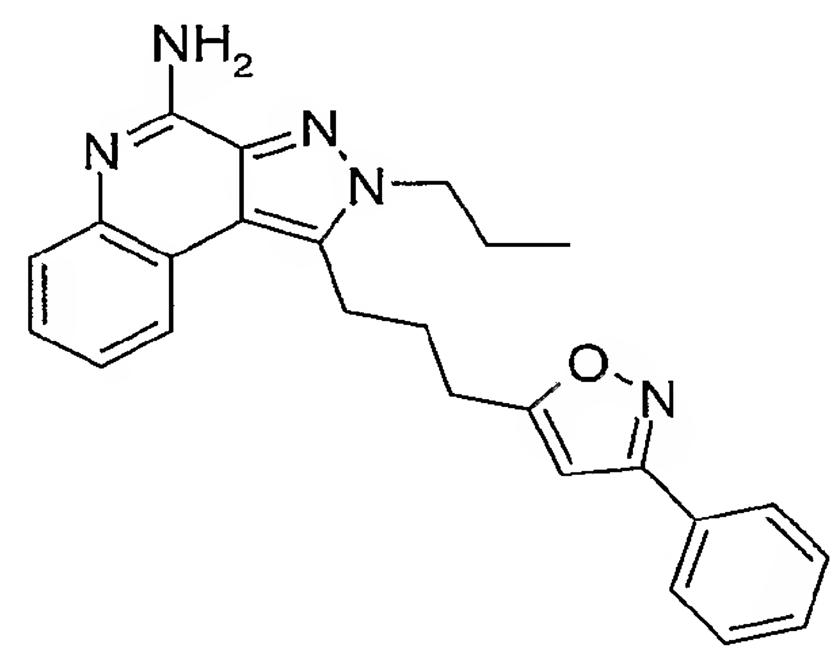
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.42 (t, J = 7.1 Hz, 1H), 7.24-7.30 (m, 1H), 5.85 (s, 1H), 5.33 (s, 2H), 4.26 (t, J = 7.3 Hz, 2H), 3.25 (t, J= 8.1 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 2.30 (s, 3H), 2.11-2.24 (m, 2H), 1.93-2.04 (m, 2H), 0.93 (t, J= 7.4 Hz, 3H);

MS (APCI) *m/z* 350 $(M + H)^+$;

Anal. calcd for $C_{20}H_{23}N_5O$: C, 68.75; H, 6.63; N, 20.04. Found: C, 68.62; H, 6.80; N, 20.00.

Example 596

1-[3-(3-Phenylisoxazol-5-yl)propyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

α-Chlorobenzaldoxime was prepared according to the method described in Part A of Example 595 by reacting benzaldoxime (11.5 g, 94.9 mmol) in DMF (20 mL) with *N*-chlorosuccinimide (12.6 g, 94.9 mmol). α-Chlorobenzaldoxime (13.7 g, 93%) was obtained as a white solid.

Part B

α-Chlorobenzaldoxime (0.64 g, 4.1 mmol) was added to a solution of di(*tert*-butyl) 1-pent-4-ynyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (prepared as described in Parts A-E of Example 57, 1.36 g, 2.76 mmol) and triethylamine (0.60 mL, 4.14 mmol) in dichloromethane (10 mL). The solution was heated at 40 °C for 19 hours, during which time additional α-chlorobenzaldoxime (0.65 g) was added. The reaction was worked up as described in Part B of Example 595. The crude product was purified by chromatography (silica gel, sequential elution with 20% then 40% ethyl acetate in

hexanes) to provide 1.35 g of di(*tert*-butyl) 1-[3-(3-phenylisoxazol-5-yl)propyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as a white solid.

Part C

A solution of the material from Part B in 6 M hydrochloric acid in ethanol (10 mL) was heated at 60 °C for 45 minutes. The reaction mixture was concentrated under reduced pressure. The residue was slurried with 1 N potassium hydroxide for 16 hours. The resulting solid was isolated by filtration, rinsed with a 6:4 mixture of hexanes/ethyl acetate, and dried at 80 ° for 3 hours to provide 0.7353 g of 1-[3-(3-phenylisoxazol-5-yl)propyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white powder, mp 176-178.0 °C.

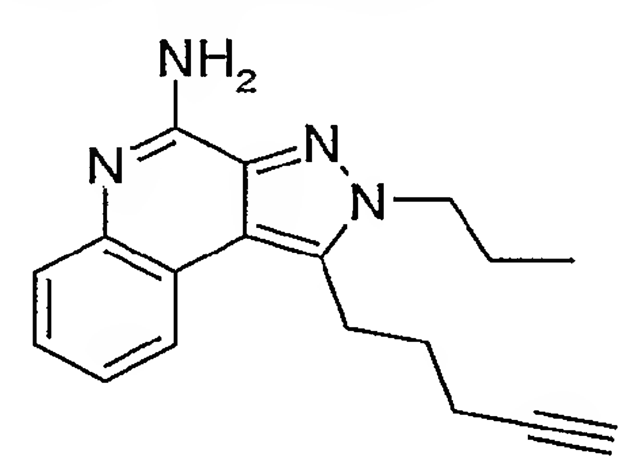
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77-7.83 (m, 3H), 7.71 (d, J = 7.4 Hz, 1H), 7.39-7.48 (m, 4H), 7.23-7.80 (m, 1H), 6.35 (s, 1H), 5.37 (s, 2H), 4.27 (t, J = 7.3 Hz, 2H), 3.32 (t, J = 8.0 Hz, 2H), 3.01 (t, J = 7.2 Hz, 2H), 2.24 (p, J = 7.6 Hz, 2H), 1.99 (q, J = 7.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H);

MS (APCI) *m/z* 412 $(M + H)^+$;

Anal. calcd for $C_{25}H_{25}N_5O \cdot 0.6\ H2O$: C, 71.10; H, 6.25; N, 16.58. Found: C, 70.93; H, 6.36; N, 16.48.

Example 597

1-Pent-4-ynyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



A solution of di(*tert*-butyl) 1-pent-4-ynyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (prepared as described in Parts A-E of Example 57, 0.400 g, 0.812 mmol) in 6 M HCl in ethanol (3 mL) was heated at 60 °C for 1.7 hours. The solution was allowed to cool to room temperature, and then was concentrated under reduced pressure to yield an oil. The oil was treated with 1 M aqueous potassium hydroxide to generate a white precipitate, which was isolated by filtration. The crude product was purified by

chromatography (silica gel, gradient elution with 5-10% CMA in chloroform) followed by crystallization from hexanes/ethyl acetate to afford 0.061 g of 1-pent-4-ynyl-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as white crystals, mp 144.0-145.0 °C.

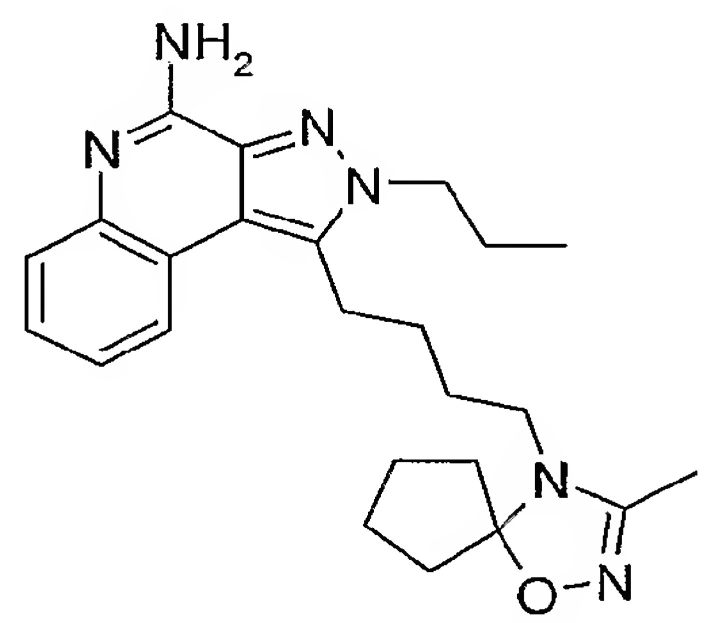
^{1}H NMR (300 MHz, DMSO) δ 7.96 (d, *J* = 7.4 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.2 Hz, 1H), 5.41 (s, 2H), 4.34 (t, *J* = 7.4 Hz, 2H), 3.35 (t, *J* = 8.0 Hz, 2H), 2.35-2.41 (m, 2H), 2.14 (t, *J* = 2.6 Hz, 1H), 1.95-2.03 (m, 4H), 1.00 (t, *J* = 7.4 Hz, 3H);

MS (APCI) *m/z* 293 $(M + H)^+$;

Anal. calcd for $C_{18}H_{20}N_4$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.58; H, 6.90; N, 19.24.

Example 598

1-[4-(3-Methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A mixture of di(*tert*-butyl) 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (prepared as described in Part A of Example 57, 6.82 g, 13.2 mmol), sodium azide (1.74 g, 26.4 mmol), and sodium iodide (0.50 g, 3.30 mmol) in DMF (20 mL) was heated at 90 °C for 21 hours. The mixture was allowed to cool to room temperature, then was poured into water (500 mL) and extracted with ethyl acetate. The organic layers were combined, washed with water and brine, dried over magnesium sulfate, filtered, concentrated under reduced pressure, and dried under vacuum to afford 6.21 g of a brown solid that was used without further purification in the next step.

Part B

A mixture of the material from Part A (6.21 g, 11.9 mmol), triphenylphosphine (4.7 g, 17.8 mmol), water (7 mL), and tetrahydrofuran (70 mL) was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure and the resulting oil was dissolved in dichloromethane. The solution was washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was placed onto a column of silica gel and was eluted with ethyl acetate, followed by 5% methanol in dichloromethane, followed by 15% methanol in dichloromethane. The appropriate fractions were combined and concentrated to afford 3.37 g of di(*tert*-butyl) 1-(4-aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate.

Part C

A mixture of di(*tert*-butyl) 1-(4-aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (1.50 g, 3.01 mmol), cyclopentanone (1 mL, 11.31 mmol), and magnesium sulfate in dichloromethane (9 mL) was stirred at room temperature for 1 day. The mixture was filtered and the filtrate was concentrated under reduced pressure; and the residue was dissolved in dichloromethane (10 mL). To the solution was added α-chloroacetaldoxime (prepared as described in Part A of Example 595, 0.56 g, 6.03 mmol). The solution was cooled to 0 °C and triethylamine (1.00 mL, 7.54 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for 1 day. The mixture was transferred to a separatory funnel, washed with an aqueous solution of potassium carbonate, water, and brine, then dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, elution with 40% hexanes in ethyl acetate) to afford a 0.75 g of material that was used in the next step.

Part D

A solution of the material from Part C (0.75 g, 1.21 mmol) in 6 M HCl in ethanol (6 mL) was heated at 60 °C for 2 hours. The solution was allowed to cool to room temperature, then was concentrated under reduced pressure to yield an oil. The oil was treated with 6 M aqueous potassium hydroxide. The aqueous solution was extracted with dichloromethane several times. The organic layers were combined, washed with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The

crude product was purified by chromatography (silica gel, gradient elution with 5-15% CMA in chloroform) to afford 0.131 g of 1-[4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl]-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white powder, mp 101.0-105.0 °C.

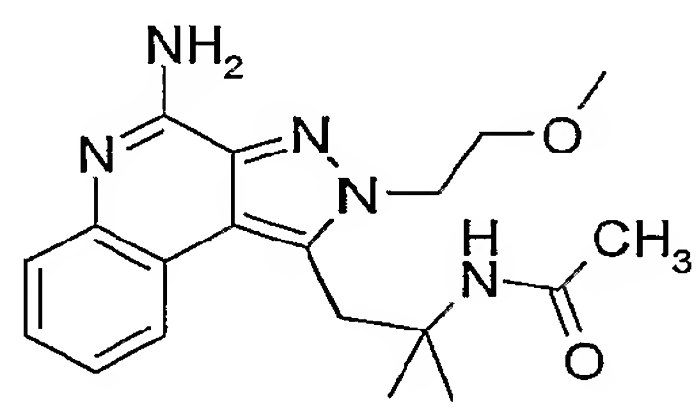
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.29 (t, J = 7.0 Hz, 1H), 5.41 (s, 2H), 4.29 (t, J = 7.3 Hz, 2H), 3.25 (t, J = 7.4 Hz, 2H), 3.03 (t, J = 7.1 Hz, 2H), 2.02 (q, J = 7.3 Hz, 2H), 1.56-1.89 (m, 15H), 1.00 (t, J = 7.4 Hz, 3H);

MS (APCI) m/z 421 $(M + H)^+$;

Anal. calcd for $C_{24}H_{32}N_6O \cdot 0.8\ H2O$: C, 66.27; H, 7.79; N, 19.32. Found: C, 66.34; H, 7.62; N, 19.21.

Example 599

N-{2-[4-Amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}acetamide

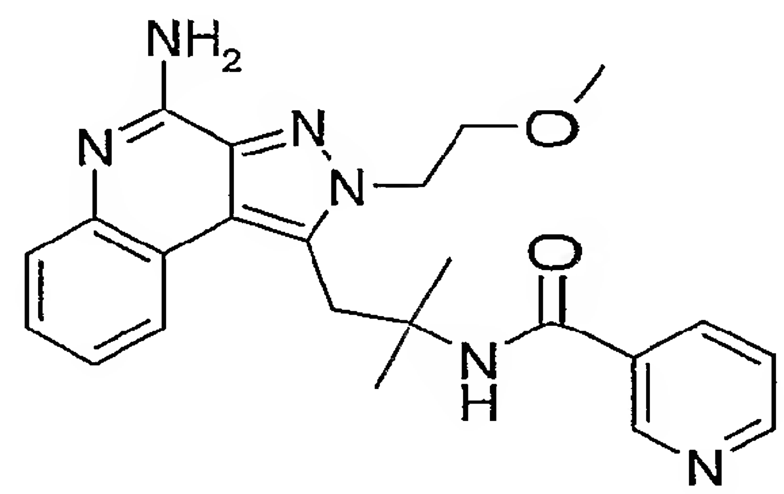


Triethylamine (5 mmol) and acetyl chloride (4.0 mmol) were added to a solution of 1-(2-amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (496 mg, 1.60 mmol, prepared as described in Example 590) in dichloromethane (20 mL). The reaction mixture was stirred for 30 minutes and then concentrated under reduced pressure. The residue was dissolved in methanol (10 mL), and then combined with concentrated hydrochloric acid (2 mL). The mixture was heated at reflux for 2 hours, diluted with 2 M aqueous sodium carbonate, and then concentrated under reduced pressure. The residue was extracted with chloroform. The extract was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by IFC (RS-90 column, eluting with a gradient of 20 to 35% CMA in chloroform) to provide 0.67 g of a colorless resin. This material was refluxed with 35% ethyl acetate in

hexanes (50 mL), cooled to ambient temperature, and then the mixture was cooled on ice. The resulting solid was isolated by filtration, rinsed with some of the solvent mix, and dried to provide 443 mg of *N*-{2-[4-amino-2-(methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}acetamide as a white solid, mp 170-171 °C. MS (ESI) m/z 356 $(M + H)^+$; Anal. Calcd for $C_{19}H_{25}N_5O_2$: C, 64.20; H, 7.09; N, 19.70. Found: C, 63.89; H, 7.41; N, 19.63.

Example 600

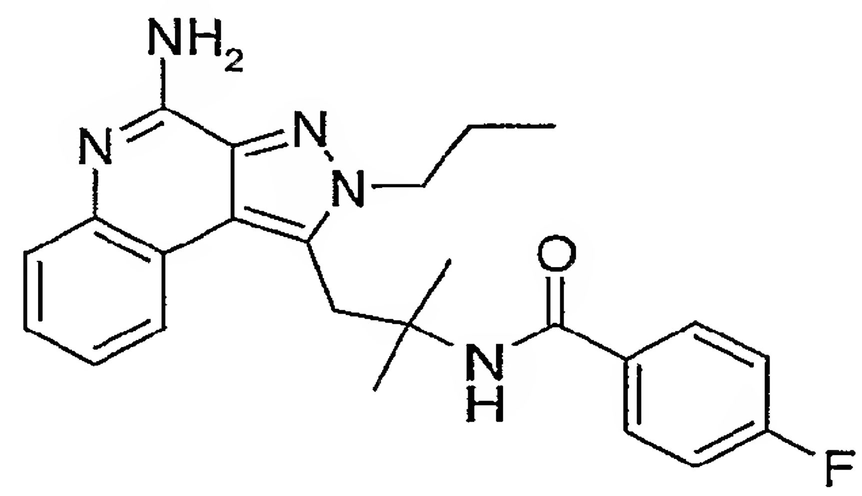
N-{2-[4-Amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}nicotinamide



Using the method of Example 68, nicotinoyl chloride hydrochloride (668 mg, 4.75 mmol) was reacted with 1-(2-amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (470 mg, 1.5 mmol, prepared as described in Example 590). The crude product was purified by IFC (silica gel eluting with a gradient of 10 to 40% CMA in chloroform) to provide a pale yellow resin. The resin was refluxed with 35% ethyl acetate in hexanes (50 mL) and ethyl acetate (75 mL) and cooled to ambient temperature with stirring. The resulting solid was isolated by filtration, rinsed with 35% ethyl acetate in hexanes, and dried to provide 278 mg of *N*-{2-[4-amino-2-(methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}nicotinamide as a light beige solid, mp 212-214 °C. MS (APCI) m/z 419 $(M + H)^+$; Anal. Calcd for $C_{23}H_{26}N_6O_2$: C, 66.01; H, 6.26; N, 20.08. Found: C, 65.74; H, 6.50; N, 20.09.

Example 601

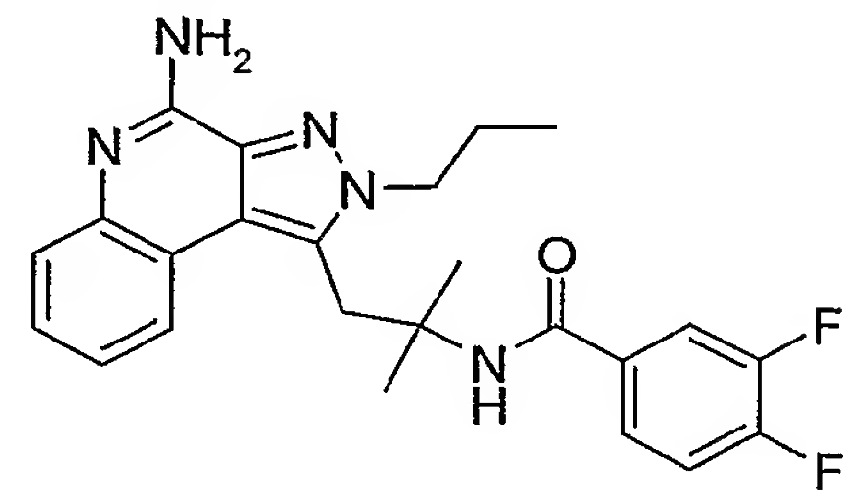
N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]-4-fluorobenzamide



Using the general method of Example 68, except that the acid chloride was added at 0 °C, 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 770 mg, 2.59 mmol) was reacted with 4-fluorobenzoyl chloride (1.03 g, 6.48 mmol) to provide 2.1 g of crude product as pale yellow resin. This material was purified by IFC (silica gel eluting with a gradient of 5 to 20% CMA in chloroform) to provide about 1 g of a white foam. The foam was stirred with 35% ethyl acetate in hexanes. The resulting solid was isolated by filtration, rinsed with the same solvent mix, and then dried to provide 503 mg of a white solid (A). The filtrate was concentrated under reduced pressure to provide a white solid. This material was dissolved in dichloromethane, precipitated with hexanes, isolated by filtration, rinsed with hexanes, and dried to provide 340 mg of a white solid (B). White solids A and B were combined, refluxed in 20% ethyl acetate in hexanes, cooled to ambient temperature, and then in an ice bath. The resulting solid was isolated by filtration, rinsed with 20% ethyl acetate in hexanes, and dried to provide 706 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]-4-fluorobenzamide as a white solid, mp 168-169 °C. MS (APCI) m/z 420 $(M + H)^+$; Anal. Calcd for $C_{24}H_{26}FN_5O$: C, 68.72; H, 6.25; N, 16.69. Found: C, 68.69; H, 6.15; N, 16.90.

Example 602

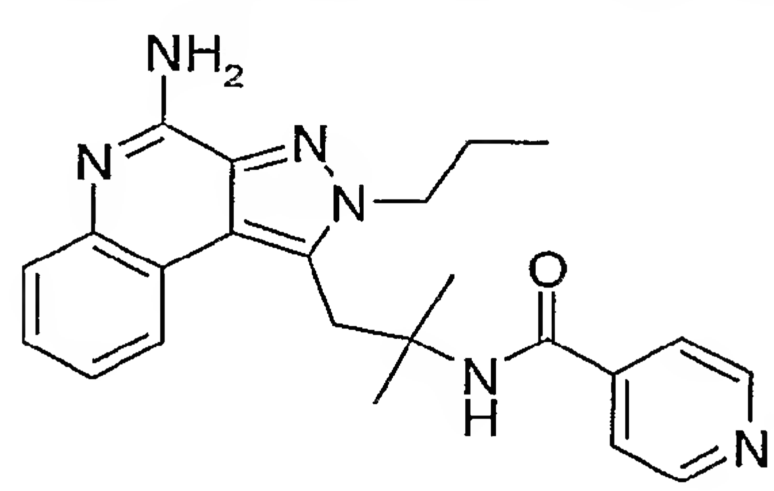
N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1 -dimethylethyl]-3,4-difluorobenzamide



Using the method of Example 601, 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 770 mg, 2.59 mmol) was reacted with 3,4-difluorobenzoyl chloride (1.14 g, 6.48 mmol). The crude product was purified as described in Example 601 to provide 896 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3,4-difluorobenzamide as a white solid, mp 165-166 °C. MS (APCI) m/z 438 $(M + H)^+$; Anal. Calcd for $C_{24}H_{25}F_2N_5O$: C, 65.89; H, 5.76; N, 16.01. Found: C, 65.84; H, 5.58; N, 15.92.

Example 603

N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]isonicotinamide

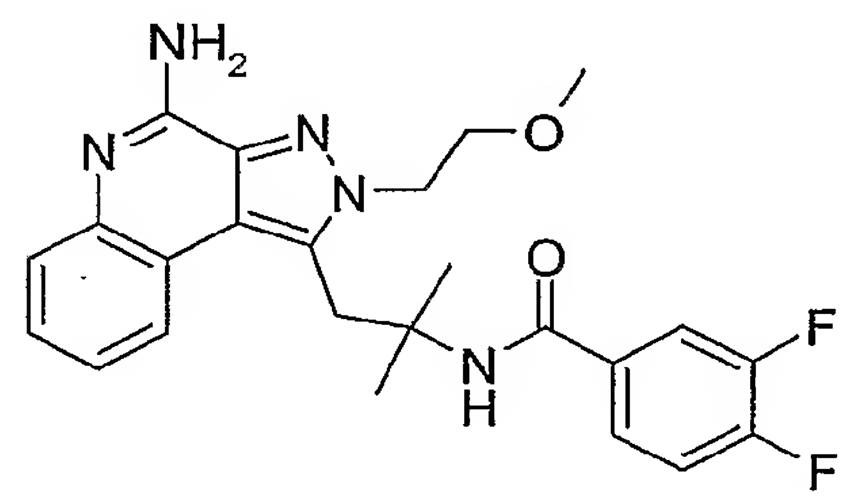


Using the method of Example 68, 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 770 mg, 2.59 mmol) was reacted with isonicotinoyl chloride hydrochloride (1.15 mg, 6.48 mmol). The crude product was purified as described in Example 68 to provide 708 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]isonicotinamide as an

off-white solid, mp 148-150 °C. MS (APCI) m/z 403 $(M + H)^+$; Anal. Cacld for $C_{23}H_{26}N_6O$: C, 68.63; H, 6.51; N, 20.88. Found: C, 68.30; H, 6.49; N, 20.92.

Example 604

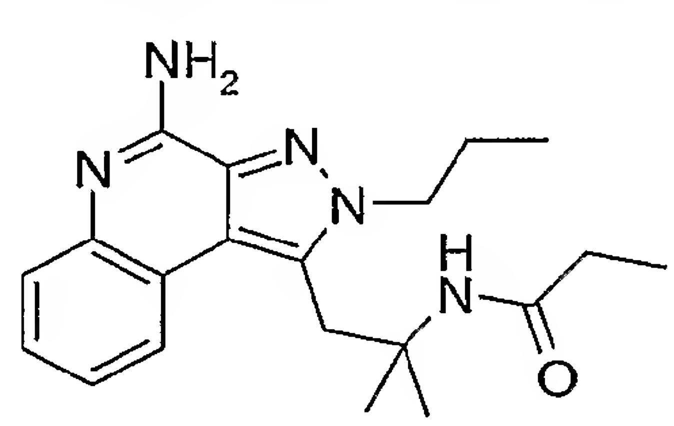
N-{2-[4-Amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}-3,4-difluorobenzamide



Using the general method of Example 599, 1-(2-amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (0.52 g, 1.66 mmol, prepared as described in Example 590) was reacted with 3,4-difluorobenzoyl chloride. The crude product was purified as described in Example 599 to provide 382 mg of *N*-{2-[4-amino-2-(methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}-3,4-difluorobenzamide as a white solid, mp 199-200 °C. MS (ESI) m/z 454 $(M + H)^+$; Anal. Calcd for $C_{24}H_{25}F_2N_5O_2$: C, 63.57; H, 5.56; N, 15.44. Found: C, 63.37; H, 5.50; N, 15.58.

Example 605

N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]propionamide

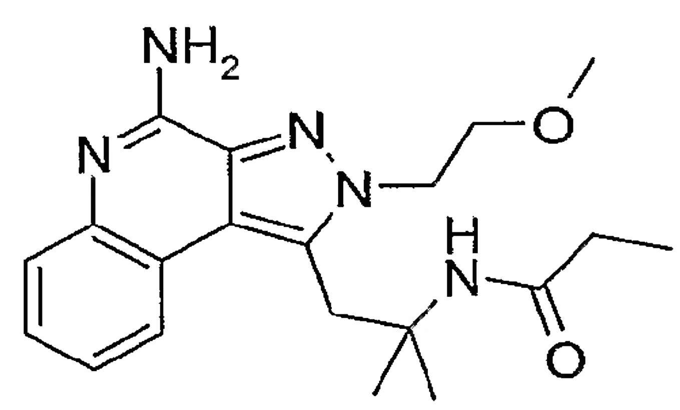


Using the method of Example 68, 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64, 595 mg, 2.00 mmol) was reacted with propionyl chloride (463 mg, 5.00 mmol). The crude product was

purified by IFC (silica gel eluting with a gradient of 15 to 25 % CMA in chloroform) followed by recrystallization from ethyl acetate/hexanes to provide 545 mg of *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]propionamide as a white solid, mp 158-159 °C. MS (APCI) m/z 354 $(M + H)^+$; Anal. Calcd for $C_{20}H_{27}N_5O$: C, 67.96; H, 7.70; N, 19.81. Found: C, 67.80; H, 8.08; N, 19.77

Example 606

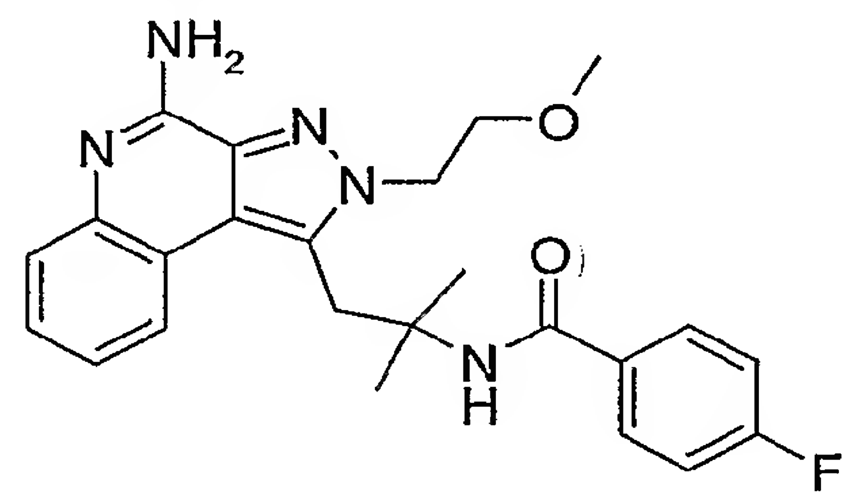
N-{2-[4-Amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}propionamide



Using the general method of Example 599, 1-(2-amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (500 mg, 1.60 mmol, prepared as described in Example 590) was reacted with propionyl chloride (370 mg, 4.00 mmol). The crude product was purified by IFC (silica gel eluting with a gradient of 15 to 50 % CMA in chloroform) followed by recrystallization from ethyl acetate/hexanes to provide 434 mg of *N*-{2-[4-amino-2-(methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}propionamide as a white solid, mp 157-158 °C. MS (APCI) m/z 370 $(M + H)^+$; Anal. Calcd for $C_{20}H_{27}N_5O_2$: C, 65.02; H, 7.37; N, 18.96. Found: C, 64.79; H, 7.58; N, 18.94.

Example 607

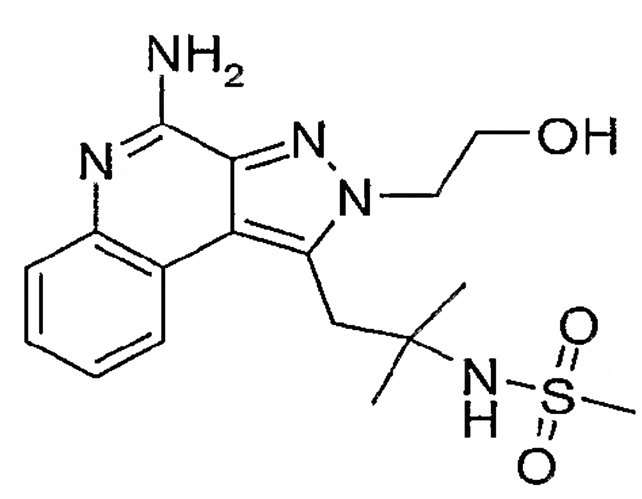
N-{2-[4-Amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}-4-fluorobenzamide



Using the general method of Example 599, 1-(2-amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (500 mg, 1.60 mmol, prepared as described in Example 590) was reacted with 4-fluorobenzoyl chloride (634 mg, 4.00 mmol). The crude product was purified by IFC (silica gel eluting with a gradient of 5 to 20 % CMA in chloroform) followed by recrystallization from ethyl acetate/hexanes to provide 551 mg of *N*-{2-[4-amino-2-(methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}-4-fluorobenzamide as a white solid, mp 187-189 °C. MS (ESI) m/z 436 $(M + H)^+$; Anal. Calcd for $C_{24}H_{26}FN_5O_2$: C, 66.19; H, 6.02; N, 16.08. Found: C, 65.92; H, 5.93; N, 15.87.

Example 608

N-{2-[4-Amino-2-(2-hydroxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide

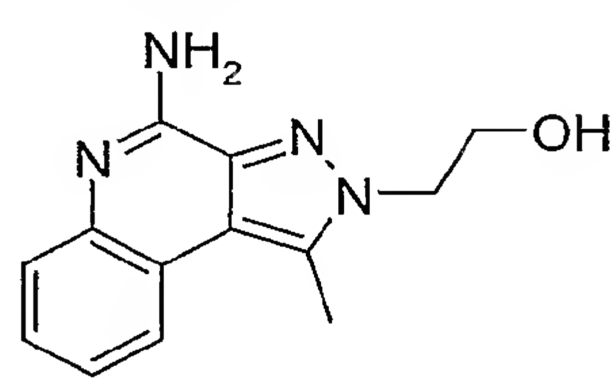


Boron tribromide (1 M in dichloromethane, 2.15 mL, 2.15 mmol) was added over a period of 2 minutes to a chilled (0 °C) slurry of *N*-{2-[4-amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide (337 mg, 0.861

mmol, prepared as described in Example 592) in dichloromethane (10 mL). The reaction mixture was stirred for 14 hours and then concentrated under reduced pressure. The residue was combined with 6 M hydrochloric acid and stirred for 3 hours. The reaction mixture was diluted with 2 M aqueous sodium carbonate. The resulting precipitate was isolated by filtration and rinsed with water and chloroform. The precipitate was combined with the chloroform layer and concentrated under reduced pressure. The residue was purified by IFC (silica gel eluting with a gradient of CMA in chloroform) followed by recrystallization from ethyl acetate/hexanes/acetonitrile to provide 184 mg of *N*-{2-[4-amino-2-(2-hydroxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}methanesulfonamide as a white solid, mp 203-204 °C. MS (ESI) m/z 378 $(M + H)^+$; Anal. Calcd for $C_{27}H_{23}N_5O_3S$: C, 54.09; H, 6.14; N, 18.55. Found: C, 54.11; H, 5.97; N, 18.42.

Example 609

2-(4-Amino-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-2-yl)ethanol



Part A

A solution of 2-hydroxyethylhydrazine (15.2 g, 200 mmol) in ethanol (50 mL) was added over a period of 30 minutes to a solution of ethyl 2,4-dioxopentanoate (31.6 g, 200 mmol) in ethanol (200 mL). The reaction mixture was stirred for an additional 20 minutes and then concentrated under reduced pressure to provide 45 g of ethyl 1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxylate a light brown oil. A portion (31.1 g) of this material was combined in a Parr vessel with methanol (25 mL) and concentrated ammonium hydroxide (25 mL). The vessel was sealed and the mixture was heated for 12 hours. The reaction mixture was concentrated under reduced pressure to provide a brown resin. The resin was stirred with a mixture of chloroform and methanol until a solid appeared. The solid was isolated by filtration and then recrystallized from isopropanol to provide 7.01 g

of 1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxamide as a white solid. The rest of the ester was purified by IFC (silica gel eluting with a gradient of 50 to 100% ethyl acetate in hexanes) to provide 6.6 g of a pale yellow oil. This material was dissolved in concentrated ammonium hydroxide (25 mL) and allowed to stand at ambient temperature for 48 hours. A precipitate was isolated by filtration, rinsed with water, and dried to provide 3.74 g of 1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxamide as white needles, mp 170-172 °C. Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.59; H, 6.65; N, 24.92.

Part B

Under a nitrogen atmosphere, triethylamine (17.9 g, 177 mmol) was added to a slurry of 1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carboxamide (7.0 g, 41.4 mmol) in dichloromethane (70 mL). The mixture was cooled in an ice bath and then a solution of trifluoroacetic anhydride (15.6 g, 74.2 mmol) in dichloromethane (70 mL) was added over a period of 10 minutes. All of the solids dissolved to provide a cloudy solution. After 1 hour additional triethylamine (70.6 mmol) was added and the reaction mixture was cooled in an ice bath. Trifluoroacetic anhydride (35.3 mmol) was added neat over a period of 5 minutes. The reaction mixture was stirred for 10 minutes then the ice bath was removed and the reaction mixture was stirred for 30 minutes. The reaction mixture was diluted with 2 M aqueous sodium carbonate (100 mL) and water (100 mL) then extracted with chloroform (x 3). The extracts were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 11.5 g of 1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carbonitrile a brown oil.

Part C

Potassium acetate (5.2 g, 53 mmol) and bromine (7.9 g, 49.4 mmol) were added sequentially to a solution of the material from Part B in acetic acid (70 mL). The reaction mixture was stirred for 20 hours and then quenched with aqueous saturated sodium bisulfite. The acetic acid was removed under reduced pressure. The residue was made basic with 2 M aqueous sodium carbonate and then extracted with chloroform (x 3). The extracts were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 11 g of a brown oil. The oil was purified by IFC (silica gel

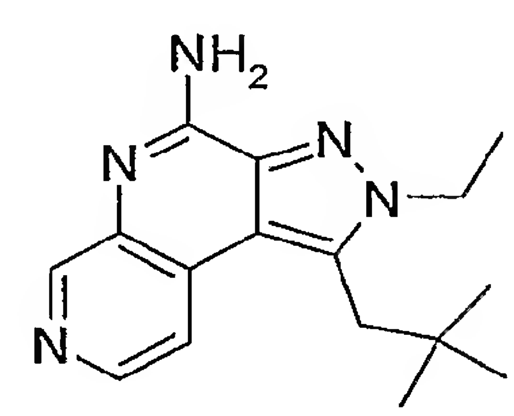
eluting with a gradient of 50 to 75 % ethyl acetate in hexanes) to provide 3.48 g of 4-bromo-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carbonitrile as a yellow oil.

Part D

2 M aqueous sodium carbonate (11.8 mL), 2-aminophenylboronic acid hydrochloride (2.04 g, 11.8 mmol), water (2.76 mL), triphenylphosphine (186 mg, 0.709 mmol), and palladium (II) acetate (53 mg, 0.236 mmol) were added sequentially to a solution of 4-bromo-1-(2-hydroxyethyl)-5-methyl-1*H*-pyrazole-3-carbonitrile (1.812 g, 7.88 mmol) in propanol (13.8 mL) in a 100 mL round bottom flask. The flask was evacuated then filled with nitrogen. The reaction mixture was heated at reflux for 22 hours. The reaction mixture was extracted with chloroform (x 4). The extracts were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a yellow oil. The oil was refluxed with *tert*-butyl methyl ether to provide about 1 g of a gummy solid. This material was purified by IFC (silica gel eluting with a gradient of 30 to 75% CMA in chloroform) to provide about 400 mg of a pale yellow solid. This material was recrystallized from acetonitrile (50 mL) to provide 187 mg of 2-(4-amino-1-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-2-yl)ethanol as a white solid, mp 226-228 °C. MS (APCI) m/z 243 $(M + H)^+$; Anal. Calcd for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.12. Found: C, 64.31; H, 6.01; N, 23.18.

Example 610

2-Ethyl-1-(2,2-dimethylpropyl)-2*H*-pyrazolo[3,4-*c*]-1,7-naphthyridin-4-amine

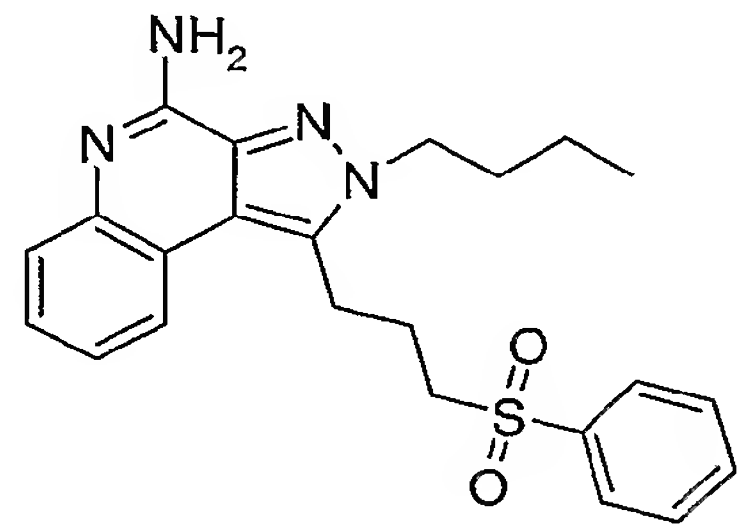


Propanol (5 mL) and 2 M hydrochloric acid (1.6 mL) were added to 3-[(*tert*-butoxycarbonyl)amino]pyridin-4-ylboronic acid (1.04 g, 4.37 mmol), prepared as described in Example 15 using *tert*-butyl *N*-(3-pyridyl)carbamate in lieu of *tert*-butyl *N*-(2-pyridyl)carbamate. The mixture was refluxed for 30 minutes to remove the BOC group. Solid sodium carbonate (710 mg, 6.7 mol), 4-bromo-1-ethyl-5-(2,2-dimethylpropyl)-1*H*-

pyrazole-3-carbonitrile (786 mg, 2.91 mmol), prepared as described in Example 38, bis[(2-diphenylphosphino)phenyl]ether (47 mg, 0.087 mmol), and palladium (II) acetate (19.5 mg, 0.087 mmol) were added. The flask was evacuated and then filled with nitrogen three times. The reaction mixture was heated at reflux for 18 hours and then partitioned between water and chloroform. The aqueous layer was extracted with chloroform (x 3). The combined organics were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a yellow oil. The oil was purified by IFC (silica gel eluting with a gradient of 2 to 45 % CMA in chloroform) to provide 180 mg of a yellow resin. This material was purified by IFC (silica gel eluting with 15% CMA in chloroform) to provide 120 mg of product. This material was refluxed in 35% ethyl acetate in hexanes (15 mL) then diluted with hexanes (15 mL) and chilled. The resulting solid was isolated by filtration and dried to provide 54 mg of a white solid. Analysis by ^{1}H NMR and IR indicated the presence of the biaryl intermediate and a nitrile group. Acetyl chloride (393 mg) and anhydrous ethanol (5 mL) were combined and stirred for 30 minutes. The white solid was added and the mixture was refluxed under nitrogen for 5 hours. The reaction mixture was allowed to stand for 48 hours; then it was diluted with 2 M aqueous sodium carbonate and concentrated under reduced pressure. The residue was extracted with chloroform (x 4). The combined extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a white solid. This material was dissolved in a minimal amount of dichloromethane and then precipitated with hexanes. The solid was isolated by filtration and dried to provide 28 mg of 2-ethyl-1-(2,2-dimethylpropyl)-2*H*-pyrazolo[3,4-*c*]-1,7-naphthyridin-4-amine as a white solid, mp > 260 °C. HRMS (ESI) Cacld for $C_{16}H_{21}N_5$ + H 284.1875, found 284.1860.

Example 611

1-(3-Benzenesulfonylpropyl)-2-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Sodium metal (23 mg, 1 mmol) was added to 25 mL of methanol. After the sodium metal was consumed, methyl acetoacetate (1.16 g, 10 mmol) was added to the mixture and stirred for 15 minutes. A solution of phenyl vinyl sulfone (1.68 g, 10 mmol) was added dropwise to the solution and maintained for several hours. The slightly yellow solution was concentrated under reduced pressure, and the residue was diluted with ethyl acetate and washed with saturated aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated to afford a clear oil. The material was purified via flash column chromatography on silica gel (eluting with hexane: ethyl acetate in a gradient from 3:2 to 2:3) to afford 1.40 g of ethyl 2-(2-benzenesulfonylethyl)-3-oxo-butyrate.

Part B

Hydrochloric acid was added (150 mL of 3 N) to a solution of ethyl 2-(2-benzenesulfonylethyl)-3-oxo-butyrate (21.7 g, 76.3 mmol) in 100 mL of ethanol and heated to reflux overnight. The reaction was cooled to ambient temperature and the mixture was concentrated under reduced pressure. The residue was extracted with several portions of ethyl acetate, and the combined organic layers were washed with saturated aqueous sodium bicarbonate, washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 16.8 g of 5-benzenesulfonylpentan-2-one as a yellow oil.

Part C

Sodium *tert*-butoxide (15.4 g, 160 mmol) was combined with ethanol (53 mL) and allowed to stir for 30 minutes. 5-Benzenesulfonylpentan-2-one (16.8 g, 74.2 mmol) and diethyl oxalate (10.1 mL, 74.2 mmol) were added to the reaction mixture in 20 mL of ethanol via an addition funnel. The reaction was maintained for 1 hour and the solution changed in color from orange to red. Potassium acetate (10.9 g, 111 mmol) was added to the reaction mixture, followed by addition of acetic acid (37 mL, 2M). The reaction mixture was then cooled to 0 °C and butyl hydrazine oxalate (13.2 g, 74.2 mmol) was added. The resultant slurry was stirred for 2 hours and turned yellow. The reaction mixture was concentrated under reduced pressure, diluted with water, and the pH of the mixture was adjusted to 11 by addition of sodium carbonate. The reaction mixture was extracted with chloroform while adding additional water to minimize elusion formation. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a red oil. The material was purified by column chromatography on silica gel (eluting with hexane: ethyl acetate in a gradient from 3:1 to 1:1) to yield 13.3 g of ethyl 5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carboxylate as an orange oil.

Part D

Sodium hydroxide (12 mL, 6M) was added to a solution of ethyl 5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carboxylate (13.3 g, 35.1 mmol) in 100 mL of ethanol and heated to reflux overnight. The reaction mixture was concentrated under reduced pressure and the residue was diluted with 100 mL of water. The aqueous layer was extracted with several portions of ethyl acetate. The pH of the aqueous layer was adjusted to approximately 2-3 with aqueous hydrochloric acid and was then extracted with several portions of ethyl acetate. The combined organic layers originating from extraction of the aqueous layer were washed with brine, dried over magnesium sulfate, filtered, and concentrated to afford 10.5 g of 5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carboxylic acid.

Part E

Oxalyl chloride (7.8 mL, 90.0 mmol) was added slowly via syringe to a solution of 5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carboxylic acid (10.5 g, 30.0 mmol)

in 100 mL of dichloromethane containing one drop of DMF. After 2 hours of stirring, saturated ammonium chloride (100 mL) was added to the reaction mixture and the reaction was maintained for 1 hour. The reaction mixture was concentrated under reduced pressure, diluted with dichloromethane and washed with water. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to afford 10.4 g of 5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carboxamide.

Part F

Phosphorus oxychloride (25 mL) was added to 5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carboxamide (10.4 g, 30.0 mmol) and heated to 90 °C for 2.5 hours. The reaction mixture was then cooled to ambient temperature and poured into ice water cooled by an ice bath. Additional ice was added to the reaction mixture and the pH of the mixture was adjusted to 8-9 by addition of 30% saturated aqueous ammonium hydroxide. The mixture was extracted with ethyl acetate and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 8.60 g of 5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carbonitrile.

Part G

Potassium acetate (3.82 g, 38.9 mmol) was added to a solution of 5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carbonitrile (8.60 g, 25.9 mmol) in 50 mL of acetic acid. The reaction mixture was stirred until all solids had dissolved, followed by dropwise addition of bromine (1.33 mL, 25.9 mmol) over 5 minutes. The resultant red solution was stirred for 5 hours and aqueous sodium thiosulfate was added to quench excess bromine. The reaction mixture was concentrated under reduced pressure and the residue was diluted with 200 mL of water. The pH of the mixture was adjusted to 8-9 by slow addition of solid sodium carbonate followed by extraction with several portions of ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford an orange oil. Purification via flash column chromatography on silica gel (eluting with hexane: ethyl acetate in a gradient from 3:1 to 1:1) afforded 4.80 g of 5-(3-benzenesulfonylpropyl)-4-bromo-1-butyl-1*H*-pyrazole-3-carbonitrile as a colorless oil that crystallized upon standing.

Part H

2-Aminophenyl boronic acid hydrochloride (693 mg, 4.00 mmol) and potassium phosphate tribasic (2.12 g, 10.0 mmol) were added sequentially to a solution of 5-(3-benzenesulfonylpropyl)-4-bromo-1-butyl-1*H*-pyrazole-3-carbonitrile (550 mg, 1.30 mmol) in 15 mL of toluene in a pressure tube. Nitrogen was bubbled through the resultant slurry for 15 minutes. Tris(dibenzylideneacetone)dipalladium(0) (104 mg, 0.10 mmol), bis[(2-diphenylphosphino)phenyl]ether (65 mg, 0.12 mmol), and 4 angstrom molecular sieves were then added to the reaction mixture. The pressure tube was sealed and heated in a 110 °C oil bath. After 20 hours, the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate and filtered through CELITE filter aid. The filtrate was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with additional ethyl acetate and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to an orange oil. Purification via flash column chromatography on silica gel (eluting with hexane: ethyl acetate in a gradient from 2:1 to 2:3) afforded 550 mg of 4-(2-aminophenyl)-5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carbonitrile as a thick pale yellow oil.

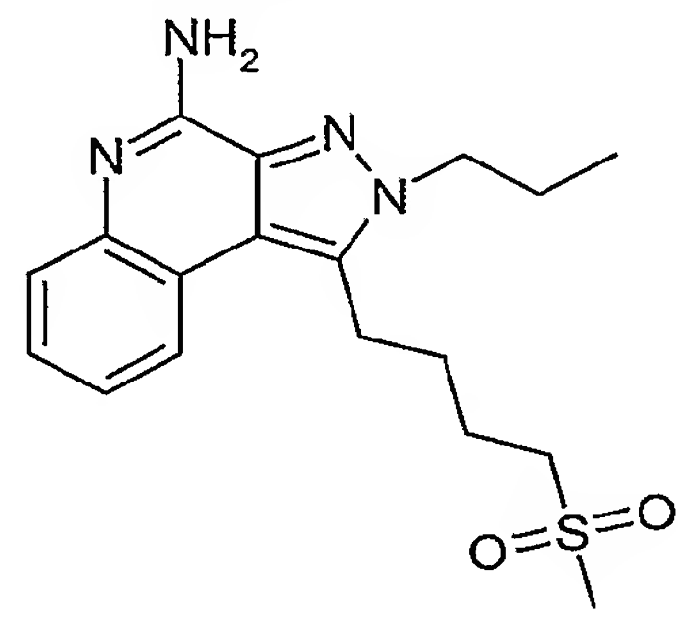
Part I

Hydrochloric acid (0.98 mL, 3.90 mmol) in ethanol was added dropwise to a solution of 4-(2-aminophenyl)-5-(3-benzenesulfonylpropyl)-1-butyl-1*H*-pyrazole-3-carbonitrile (550 mg, 1.30 mmol) in 10 mL of ethanol. The resultant solution was stirred for 2 hours, concentrated under reduced pressure, and diluted with water. The pH of the mixture was adjusted to 8-9 by slow addition of solid sodium carbonate. The aqueous layer was extracted with several portions of dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a pale yellow solid. The material was purified via flash column chromatography on silica gel (eluting with a 97:3 mixture of dichloromethane/methanol) to afford 350 mg of 1-(3-benzenesulfonylpropyl)-2-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white crystalline solid, mp 206-207 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 6.9 Hz, 2H), 7.77 (dd, J = 1.2, 8.1 Hz, 1H), 7.69 (dd, J = 0.9, 8.1 Hz, 1H), 7.63 (m, 1H), 7.53 (m, 2H), 5.37 (br s, 2H), 4.35 (app t, J = 7.2 Hz, 2H), 3.45 (m, 2H), 3.22 (t, J = 7.1 Hz, 2H), 2.23 (m, 2H), 1.94 (m, 2H), 1.40 (qd, J = 7.2, 14.6

Hz, 2H), 0.98 (t. $J = 7.3$ Hz, 3H); MS (APCI) m/z 423 ($M + H^+$); Anal. calcd for $C_{23}H_{26}N_4O_2S$: C, 65.38; H, 6.20; N, 13.26. Found: C, 65.40; H, 6.01; N, 13.26.

Example 612

1-(4-Methanesulfonylbutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

2-Aminophenyl boronic acid hydrochloride (9.10 mg, 26.3 mmol) and freshly ground potassium phosphate tribasic (27.8 g, 131 mmol) were added sequentially to a solution of 4-bromo-5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carbonitrile (8.00 g, 26.3 mmol), prepared as described in Example 46, in 100 mL of toluene in a pressure tube. Nitrogen was bubbled through the resultant slurry for 15 minutes. Tris(dibenzylideneacetone)dipalladium(0) (1.36 g, 1.31 mmol), bis[(2-diphenylphosphino)phenyl]ether (851 mg, 1.58 mmol), and 4 angstrom molecular sieves were then added to the reaction mixture. The pressure tube was sealed and heated in a 110 °C oil bath. After 24 hours, the reaction mixture was cooled to ambient temperature, diluted with ethyl acetate and filtered through CELITE filter aid. The filtrate was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate. The aqueous layer was extracted with additional ethyl acetate and the combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated to a red oil. Purification via flash column chromatography on silica gel (eluting with 2:1 hexane: ethyl acetate) afforded 7.60 g of 4-(2-aminophenyl)-5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carbonitrile as a red oil.

Part B

Hydrochloric acid (18 mL, 71.0 mmol) in ethanol was added dropwise to a solution of 4-(2-aminophenyl)-5-(4-chlorobutyl)-1-propyl-1*H*-pyrazole-3-carbonitrile (7.50g, 23.7 mmol) in 150 mL of ethanol. The resultant solution was heated to reflux overnight, concentrated under reduced pressure, and diluted with water. The pH of the mixture was adjusted to 9-10 by slow addition of solid sodium carbonate. The aqueous layer was extracted with several portions of dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a reddish solid. The material was purified via flash column chromatography on silica gel (eluting with a 96:4 mixture of dichloromethane/methanol) to afford 4.78 g of 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine.

Part C

Sodium thiomethoxide (0.3 g, 3.79 mmol) was added to a solution of 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (1.0 g, 3.16 mmol) in 15 mL of DMF and heated for 3 hours at 80 °C. The reaction mixture was allowed to cool to ambient temperature, diluted with dichloromethane, and washed with water. The aqueous layer was extracted with several additional portions of dichloromethane and the combined organic layers were washed with water, washed with brine, dried over magnesium sulfate, and concentrated to afford 1.04 g of 1-(4-methylthiobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a yellow solid.

Part D

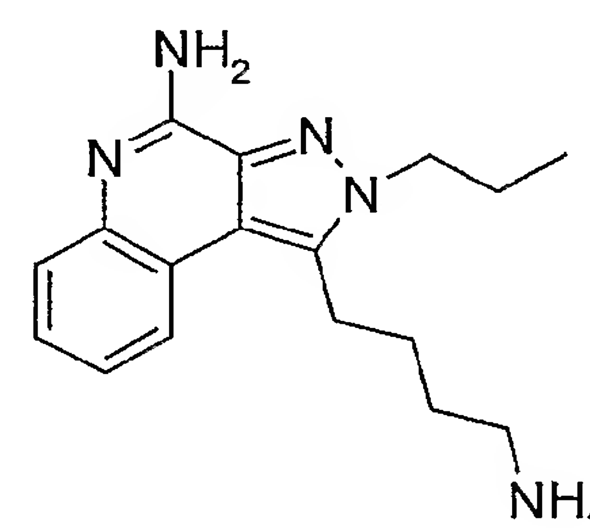
3-Chloroperoxybenozic acid (mCPBA) (75% pure, 1.60 g, 6.97 mmol, 2.2 eq) was added portion wise to a solution of 1-(4-methylthiobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (1.04 g, 3.16 mmol) in 50 mL of chloroform over several minutes. The resulting reaction mixture was stirred at ambient temperature for 2 hours and became darker red in color. The mixture was then washed with saturated aqueous sodium bicarbonate, the layers were separated, and the aqueous layer was further extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a dark oil. The material was purified via flash column chromatography on silica gel (eluting with dichloromethane/methanol in a gradient from 97:3 to 93:7), diluted with acetonitrile,

washed with saturated aqueous sodium bicarbonate, and purified a second time via flash column chromatography on silica gel (eluting with dichloromethane/methanol in a gradient from 97:3 to 93:7). The product was recrystallized from acetonitrile to afford 960 mg of 1-(4-methanesulfonylbutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a yellow crystalline solid, mp 155-157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 1H), 7.73 (dd, J = 1.2, 8.1 Hz, 1H), 7.46 (dt, J = 1.2, 6.9 Hz, 1H), 7.32 (dt, J = 1.2, 7.5 Hz, 1H), 5.54 (br s, 2H), 4.31 (t, J = 7.2 Hz, 2H), 3.29 (t, J = 7.5 Hz, 2H), 3.07 (t, J = 7.5 Hz, 2H), 2.90 (s, 3H), 2.12-1.93 (m, 6H), 1.02 (t, J = 7.2 Hz, 3H); MS (APCI) m/z 361 ($M + H^+$); Anal. calcd for $C_{18}H_{24}N_4O_2S$ (containing 0.5 CH_3CN): C, 59.90; H, 6.75; N, 16.54. Found: C, 59.89; H, 6.83; N, 16.77.

Example 613

Alternative preparation of

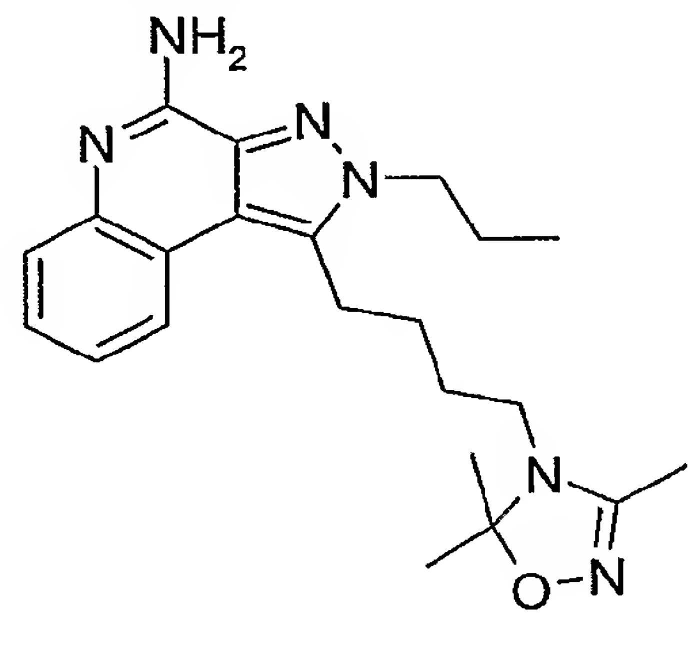
1-(4-Aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Using the method of Example 593, the protecting groups were removed from di(*tert*-butyl) 1-(4-aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (0.368 mg), prepared as described in Example 598. The crude product was purified by column chromatography (silica gel eluting with chloroform/CMA in a gradient of 95:5 to 8:2) to provide 0.0993 g of 1-(4-aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white powder, mp 156.0-157.0 °C. ^{1}H NMR (500 MHz, DMSO-d6) δ 7.90 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.19 (t, J = 8.1 Hz, 1H), 6.62 (s, 2H), 4.34 (t, J = 7.3 Hz, 2H), 3.23 (t, J = 7.8 Hz, 2H), 2.69 (t, J = 6.9 Hz, 2H), 1.92 (t, J = 7.3 Hz, 2H), 1.67-1.71 (m, 2H), 1.49-1.57 (m, 4H), 0.92 (t, J = 7.4 Hz, 3H); MS (APCI) m/z 298 $(M + H)^+$; Anal. calcd for $C_{17}H_{23}N_5 \cdot 0.3\ H_2O$: C, 67.43; H, 7.86; N, 23.13. Found: C, 67.61; H, 7.98; N, 23.20.

Example 614

2-Propyl-1-[4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

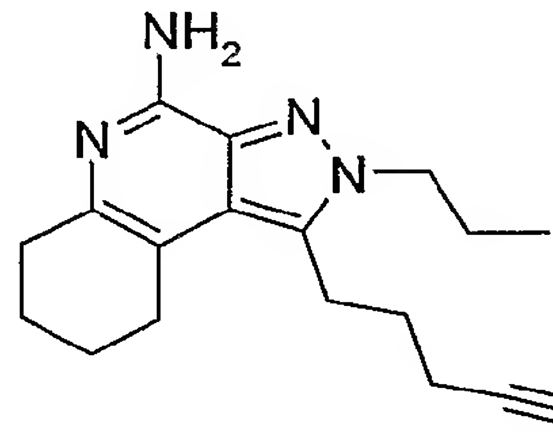
Using the general method of Example 598 Part C, di(*tert*-butyl) 1-(4-aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (1.50 g, 3.01 mmol), prepared as described in Example 598, was reacted with acetone to form an imine intermediate and the imine was treated with α-chloroacetaldoxime. The crude product was purified by chromatography (silica gel, elution with a gradient of 40 to 80% ethyl acetate in hexanes) to provide 0.66 g of di(*tert*-butyl) 2-propyl-1-[4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as a white solid.

Part B

The Boc protecting groups were removed from the material from Part A by acid hydrolysis as described in Example 598 Part D. The crude product was purified by chromatography (silica gel, elution with 9:1 chloroform/CMA) and dried under high vacuum at 65 °C to provide 0.0874 g of 2-propyl-1-[4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl]-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white solid, mp 144.0-146.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.3 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 5.44 (s, 2H), 4.22 (t, *J* = 7.3 Hz, 2H), 3.18 (t, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.9 Hz, 2H), 1.94 (q, *J* = 7.3 Hz, 2H), 1.63-1.77 (m, 7H), 1.32 (s, 6H), 0.93 (t, *J* = 7.4 Hz, 3H); MS (APCI) *m/z* 395 $(M + H)^+$; Anal. calcd for $C_{22}H_{30}N_6O \cdot 0.3\ H2O$: C, 66.07; H, 7.71; N, 21.01. Found: C, 65.82; H, 7.74; N, 20.90.

Example 615

1-Pent-4-ynyl-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

A mixture of 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (19.45 g, 61.39 mmol), prepared as described in Example 46, platinum oxide (10.00 g) and trifluoroacetic acid (200 mL) was placed under hydrogen pressure (50 psi, 3.4×10^5 Pa) for 2 days. The reaction mixture was filtered through CELITE filter aid. The filtrate was concentrated under reduced pressure to provide a dark oil. The oil was chilled in an ice bath, ice was added, and the mixture was made basic (pH 14) by the addition of 1 N potassium hydroxide. The resulting solid was isolated by filtration and then dissolved in dichloromethane. The solution was washed sequentially with 1 N potassium hydroxide, water, and brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was dried under vacuum for 2 days to provide 18.0 g of 1-(4-chlorobutyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as an oil.

Part B

Using the method of Example 57 Part A, the material from Part A was reacted with di-*tert*-butyl dicarbonate (49 g, 4 eq) to provide a quantitative yield of di(*tert*-butyl) 1-(4-chlorobutyl)-2-propyl-6,7,8,9-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as a black oil.

Part C

Using the method of Example 57 Part B, the material from Part B was reacted with potassium acetate (11.0 g, 2.0 eq) to provide 29.25 g of 4-{4-[bis(*tert*-butoxycarbonyl)amino]-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl}butyl acetate as a black oil.

Part D

Using the method of Example 57 Part C, the acetate protecting group was removed from the material from Part C to provide 24.2 g of di(*tert*-butyl) 1-(4-hydroxybutyl)-2-

propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as a brown solid.

Part E

The material from Part D was oxidized using the method of Example 57 Part D. The crude product was purified by chromatography (silica gel, elution with 1:1 hexanes/ethyl acetate) and dried under vacuum at ambient temperature over the weekend to provide 15.5 g of di(*tert*-butyl) 1-(4-oxobutyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as an amber, glassy, semi-solid.

Part F

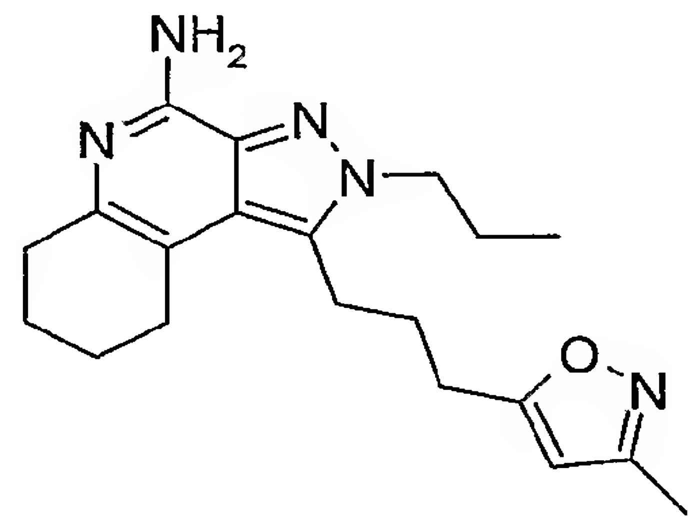
Using the method of Example 58 Part E, the material from Part E was reacted with freshly prepared diethyl 1-diazo-2-oxopropylphosphonate (10.22 g, 1.5 eq) to provide 15.33 g of di(*tert*-butyl) 1-pent-4-ynyl-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as a tan solid.

Part G

Under a nitrogen atmosphere, a solution of a portion (0.75 g) of the material from Part F in 6 M hydrochloric acid in ethanol (10 mL) was heated at 60 °C for 1.7 hours. The reaction mixture was concentrated under reduced pressure. The residue was made basic with 1 N potassium hydroxide and then extracted with dichloromethane. The combined extracts were washed sequentially with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, elution with a gradient of 5 – 20% CMA in chloroform) to provide 0.327 g of a tan solid. This material was twice triturated with boiling diethyl ether and isolated by filtration to provide 0.2823 g of 1-pent-4-ynyl-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white solid, mp 167.0-169.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.07 (s, 2H), 4.25 (t, J = 7.5 Hz, 2H), 3.15 (t, J = 8.1 Hz, 2H), 2.81-2.84 (m, 2H), 2.64-2.70 (m, 2H), 2.22-2.29 (m, 2H), 2.00 (t, J = 2.5 Hz, 1H), 1.99 (q, J = 7.4 Hz, 2H), 1.81-1.87 (m, 6H), 0.97 (t, J = 7.4 Hz, 3H); MS (APCI) m/z 297 $(M + H)^+$; Anal. calcd for $C_{18}H_{24}N_4 \cdot 0.3H_2O$: C, 71.63; H, 8.22; N, 18.56. Found: C, 71.60; H, 7.96; N, 18.71.

Example 616

1-[3-(3-Methylisoxazol-5-yl)propyl]-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

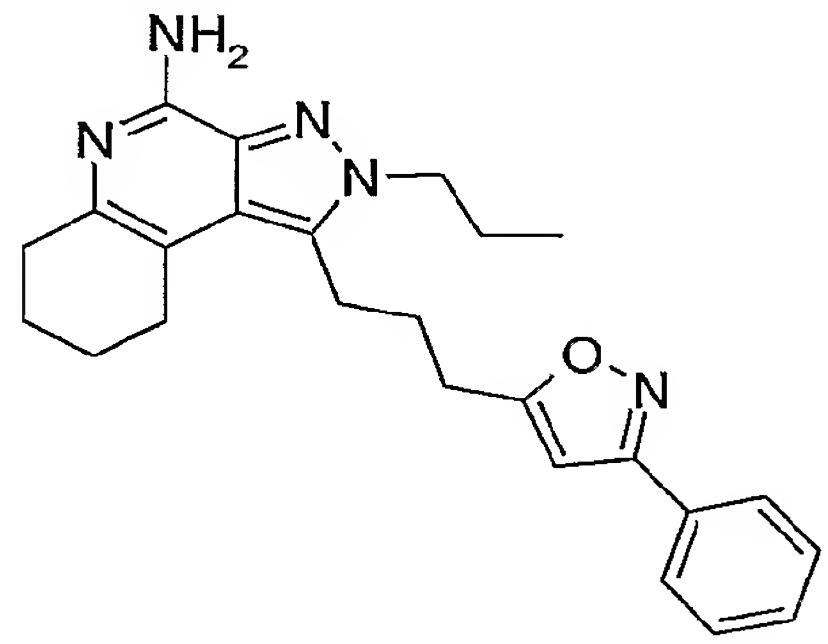
Using the method of Example 595 Part B, di(*tert*-butyl) 1-pent-4-ynyl-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (4.00 g, 8.05 mmol), prepared as described in Example 615, was reacted with α-chloroacetaldoxime (1.13 g, 12.1 mmol). The crude product was purified by chromatography (silica gel, elution with a gradient of 20 – 40% ethyl acetate in hexanes) to provide 1.55 g of di(*tert*-butyl) 1-[3-(3-methylisoxazol-5-yl)propyl]-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as a glassy solid.

Part B

Under a nitrogen atmosphere, a solution of the material from Part A in 6 M hydrochloric acid in ethanol (10 mL) was heated at 60 °C for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was made basic with 1 N potassium hydroxide and then extracted with dichloromethane. The combined extracts were washed sequentially with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was dried under vacuum over the weekend and then triturated with a mixture of hexanes and diethyl ether. The resulting solid was isolated by filtration and dried to provide 0.3342 g of 1-[3-(3-methylisoxazol-5-yl)propyl]-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white solid, mp 144.0-145.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (s, 1H), 5.06 (bs, 2H), 4.17 (t, J = 7.4 Hz, 2H), 3.05 (t, J = 8.1 Hz, 2H), 2.79-2.86 (m, 4H), 2.71-2.75 (m, 2H), 2.28 (s, 3H), 1.89-2.07 (m, 4H), 1.80-1.84 (m, 4H), 0.95 (t, J = 7.4 Hz, 3H); MS (APCI) m/z 354 $(M + H)^+$; Anal. calcd for $C_{20}H_{27}N_5O$: C, 67.96; H, 7.70; N, 19.81. Found: C, 67.67; H, 7.83; N, 19.68.

Example 617

1-[3-(3-Phenylisoxazol-5-yl)propyl]-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

Under a nitrogen atmosphere, a mixture of di(*tert*-butyl) 1-pent-4-ynyl-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (4.00 g, 8.05 mmol), prepared as described in Example 615, α-chlorobenzaldoxime (2.51 g, 16.1 mmol), prepared as described in Example 596, anhydrous triethylamine (1.7 mL, 12.1 mmol), and anhydrous dichloromethane (25 mL) was heated at 40 °C for 18 hours. The reaction mixture was diluted with dichloromethane, washed sequentially with potassium carbonate, water, and brine, dried over sodium sulfate, and filtered. The filtrate was loaded onto a silica gel column (250 g) and eluted with a gradient of 30 – 40% ethyl acetate in hexanes. The fractions containing product were combined and concentrated under reduced pressure to provide 2.97 g of di(*tert*-butyl) 1-[3-(3-phenylisoxazol-5-yl)propyl]-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate as a pale yellow solid.

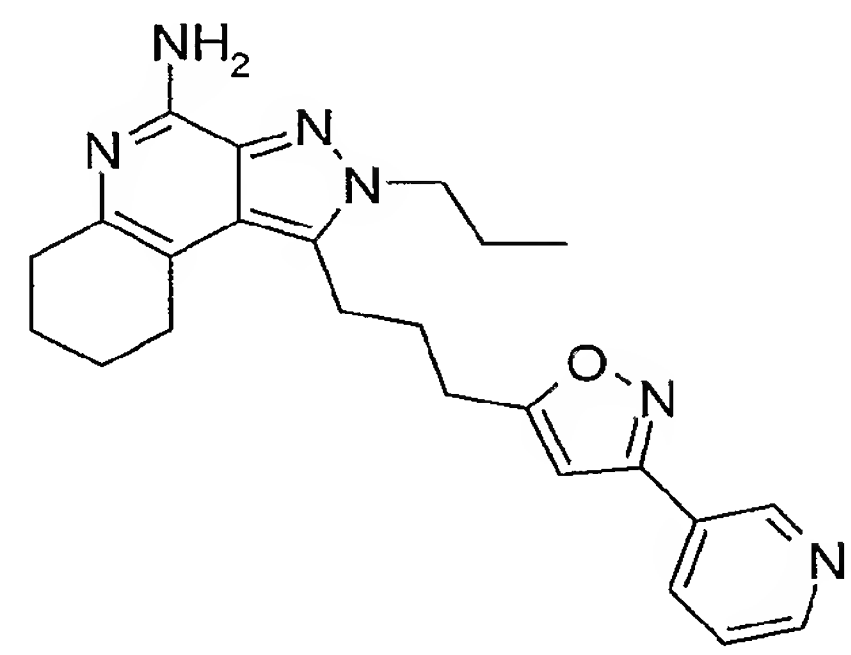
Part B

Under a nitrogen atmosphere, a solution of the material from Part A in 6 M hydrochloric acid in ethanol (20 mL) was heated at 60 °C for 1.7 hours. The reaction mixture was concentrated under reduced pressure. The residue was made basic with 1 N potassium hydroxide and then extracted with dichloromethane. The combined extracts were washed sequentially with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 1.75 g of a yellow solid. This material was purified by column chromatography (silica gel, elution with a gradient of 10 – 20% CMA in chloroform) to provide 1.324 g of product. This material was triturated twice with hot

diethyl ether to provide 0.85 g of a pale yellow solid. The solid was recrystallized twice from ethanol to provide 1-[3-(3-phenylisoxazol-5-yl)propyl]-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white solid, mp 154.0-155.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75-7.80 (m, 2H), 7.42-7.49 (m, 3H), 6.34 (s, 1H), 5.01 (bs, 2H), 4.19 (t, J = 7.4 Hz, 2H), 3.11 (t, J = 8.2 Hz, 2H), 2.94 (t, J = 7.3 Hz, 2H), 2.83 (m, 2H), 2.73 (m, 2H), 2.09 (p, J = 8.0 Hz, 2H), 1.95 (q, J = 7.4 Hz, 2H), 1.80-1.84 (m, 4H), 0.95 (t, J = 7.4 Hz, 3H); MS (APCI) m/z 416 $(M + H)^+$.

Example 618

2-Propyl-1-[3-(3-pyridin-3-ylisoxazol-5-yl)propyl]-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine



Part A

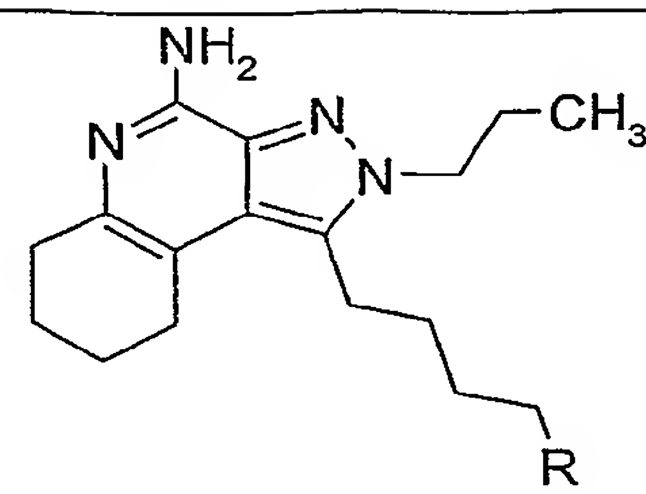
Under a nitrogen atmosphere, *N*-chlorosuccinimide (2.1 g, 16 mmol) was added to a solution of 3-pyridine aldoxime (2.0 g, 16 mmol) in THF (10 mL). The solution was stirred at ambient temperature for 4 hours. A solution of di(*tert*-butyl) 1-pent-4-ynyl-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate (4.00 g, 8.05 mmol), prepared as described in Example 615, and anhydrous triethylamine (2.5 mL, 18 mmol) in THF (10 mL) was added and the reaction solution was heated at 60 °C for 18 hours. The reaction solution was concentrated under reduced pressure to provide a black oil. The oil was dissolved in dichloromethane, washed sequentially with potassium carbonate, water, and brine, dried over sodium sulfate, and filtered. The filtrate was purified by column chromatography (silica gel, elution with a gradient of 20 – 80% ethyl acetate in hexanes) to provide 1.0877 g of di(*tert*-butyl) 2-propyl-1-[3-(3-pyridin-3-ylisoxazol-5-yl)propyl]-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-ylimidodicarbonate.

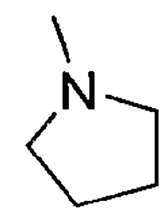
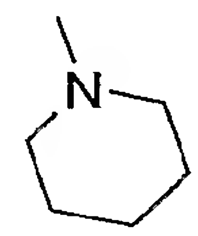
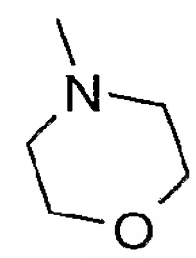
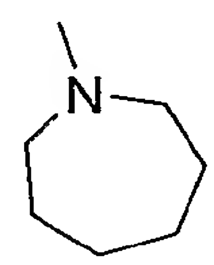
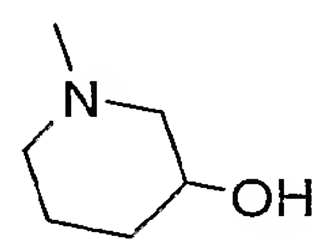
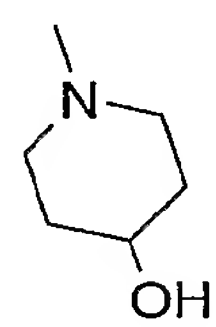
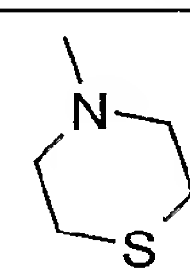
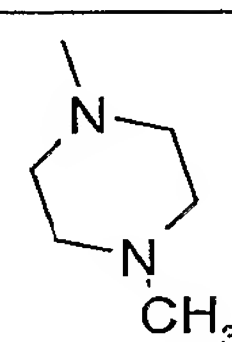
Part B

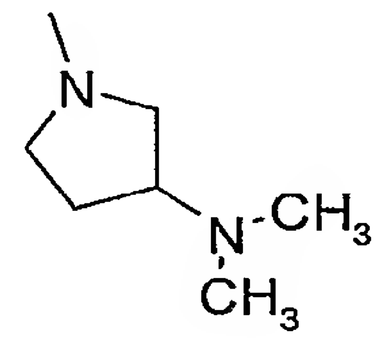
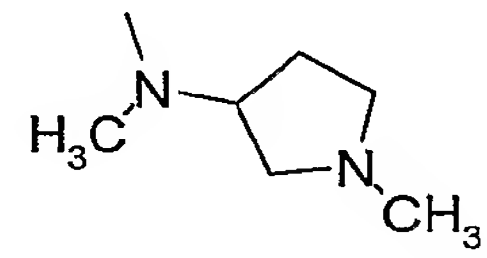
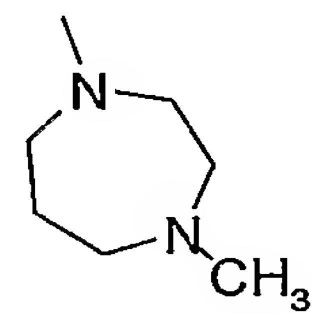
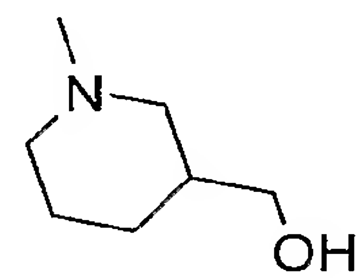
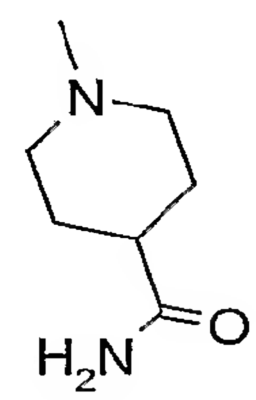
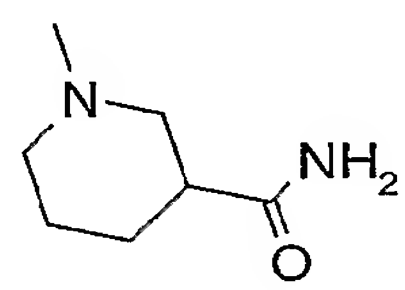
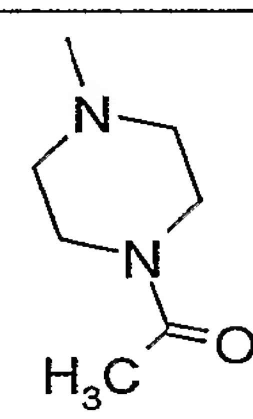
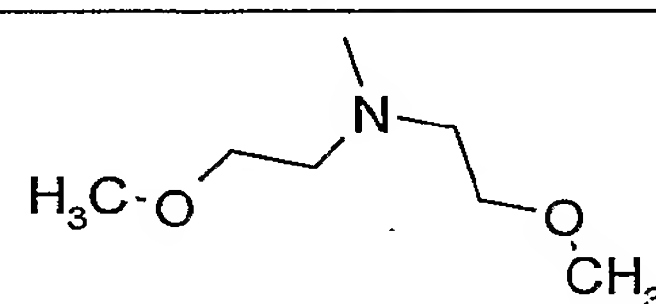
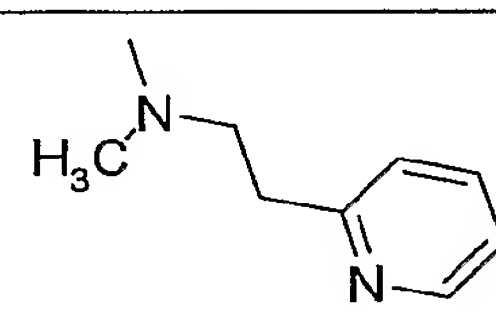
Under a nitrogen atmosphere, a solution of the material from Part A in 6 M hydrochloric acid in ethanol (20 mL) was heated at 60 °C for 1.5 hours. The reaction mixture was concentrated under reduced pressure. The residue was made basic with 1 N potassium hydroxide and then extracted with dichloromethane. The combined extracts were washed sequentially with water and brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, elution with a gradient of 5 – 20% CMA in chloroform) to provide 0.385 g of product. This material was triturated twice with hot diethyl ether to provide 0.2185 g of 2-propyl-1-[3-(3-pyridin-3-ylisoxazol-5-yl)propyl]-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a white solid, mp 168.0-170.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.98-9.01 (md, 1H), 8.68-8.7 (mt, 1H), 8.11-8.15 (md, 1H), 7.38-7.43 (m, 1H), 6.38 (s, 1H), 5.17 (bs, 2H), 4.20 (t, J = 7.3 Hz, 2H), 3.12 (t, J = 8.2 Hz, 2H), 2.97 (t, J = 7.3 Hz, 2H), 2.80-2.85 (m, 2H), 2.70-2.75 (m, 2H), 2.11 (p, J = 8.0 Hz, 2H), 1.96 (q, J = 7.4 Hz, 2H), 1.70-1.89 (m, 4H), 0.96 (t, J = 7.4 Hz, 3H); MS (APCI) m/z 417 $(M + H)^+$; Anal. calcd for $C_{24}H_{28}N_6O \cdot 0.6H_2O$: C, 67.46; H, 6.89; N, 19.67. Found: C, 67.19; H, 6.61; N, 19.65.

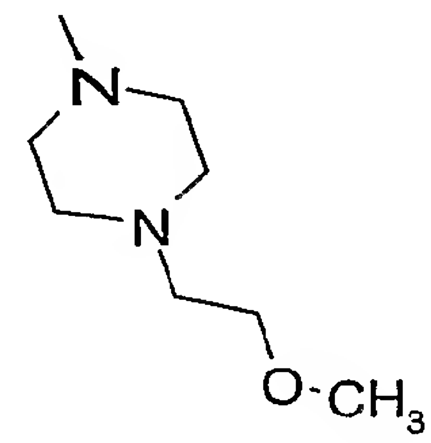
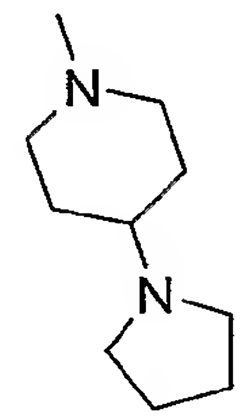
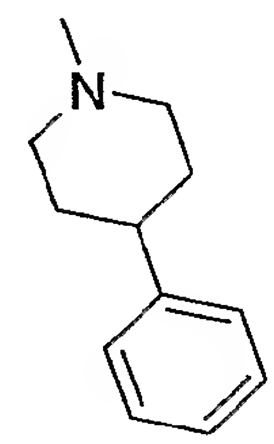
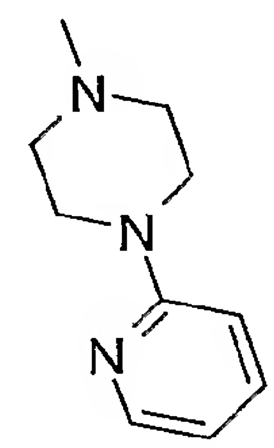
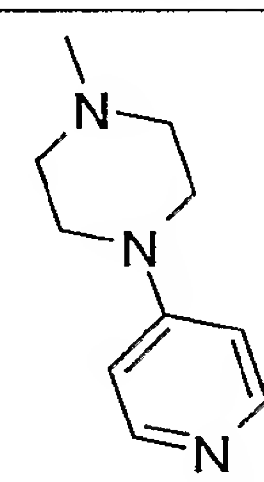
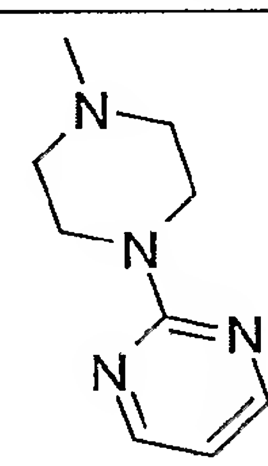
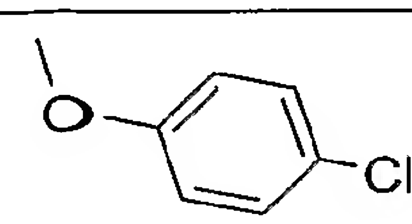
Examples 619 – 643

A reagent (0.15 mmol, 1.5 equivalents) from the table below was added to a test tube containing 1-(4-chlorobutyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine (32 mg, 0.10 mmol, prepared as described in Example 615 Part A) and potassium carbonate (approximately 55 mg, 0.40 mmol) in *N,N*-dimethylacetamide (1 mL). The test tubes were capped and heated at 90 °C for approximately 16 hours. The reaction mixtures were filtered and the solvent was removed from the filtrates by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
619	None – starting material		321.1830
620	Pyrrolidine		356.2833
621	Piperidine		370.2978
622	Morpholine		372.2796
623	Hexamethyleneimine		384.3158
624	3-Hydroxypiperidine		386.2952
625	4-Hydroxypiperidine		386.2952
626	Thiomorpholine		388.2558
627	1-Methylpiperazine		385.3067

628	3-(Dimethylamino)pyrrolidine		399.3262
629	*N,N'*-Dimethyl-3-aminopyrrolidine		399.3273
630	*N*-Methylhomopiperazine		399.3264
631	3-(Hydroxymethyl)piperidine		400.3107
632	Isonipecotamide		413.3041
633	Nipecotamide		413.3047
634	1-Acetylpiperazine		413.3029
635	bis(2-Methoxyethyl)amine		418.3217
636	2-(2-Methylaminoethyl)pyridine		421.3109

637	1-(2-Methoxyethyl)piperazine		429.3309
638	4-(1-Pyrrolidinyl)-piperidine		439.3506
639	4-Phenylpiperidine		446.3255
640	1-(2-Pyridyl)piperazine		448.3183
641	1-(4-Pyridyl)-piperazine		448.3232
642	1-(2-Pyrimidyl)piperazine		449.3107
643	4-Chlorophenol		413.2120

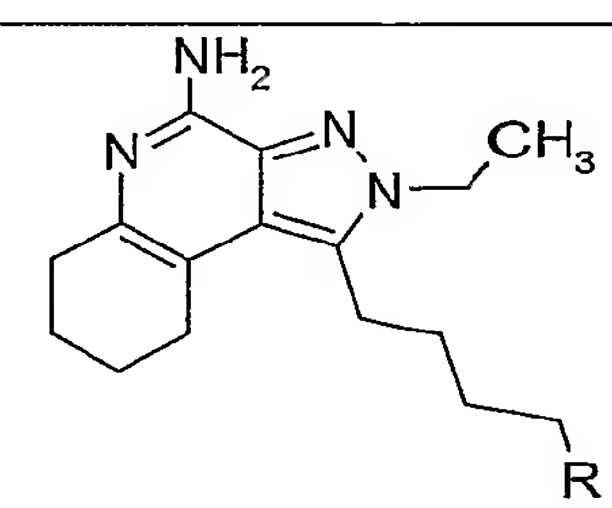
Examples 644 – 700

Part A

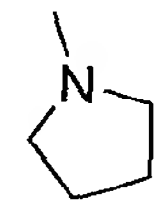
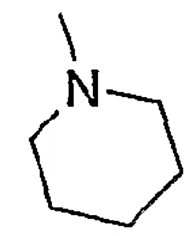
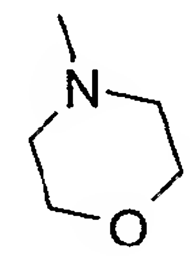
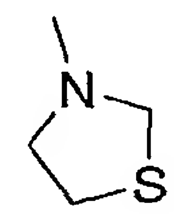
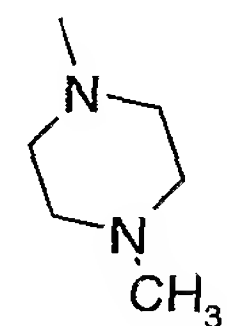
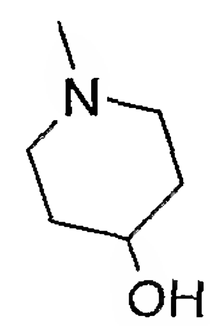
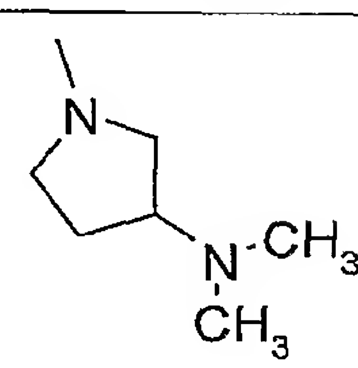
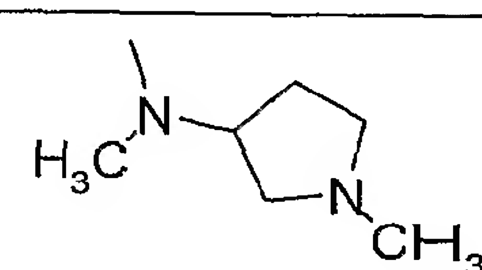
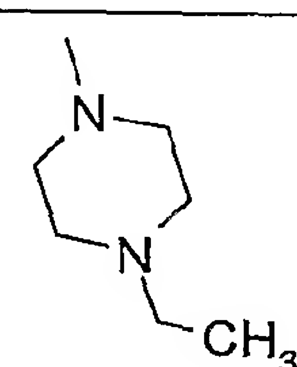
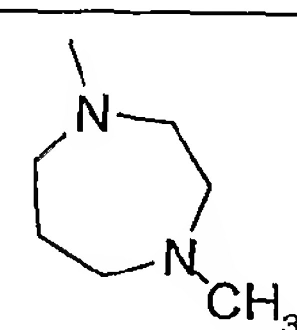
A mixture of 1-(4-chlorobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (3 g, prepared as described in Example 19), platinum (IV) oxide (3 g), and trifluoroacetic acid (50 mL) was placed under hydrogen pressure (50 psi, 3.4 X 10^5 Pa) on a Parr shaker for 2 days. The reaction mixture was filtered through a layer of CELITE filter agent and the filter cake was rinsed with dichloromethane. The filtrate was concentrated under reduced pressure. The residue was made basic (p H 14) by the addition of 50% sodium hydroxide and then extracted with chloroform. The extract was dried over sodium sulfate and then purified by chromatography on a HORIZON HPFC system (eluting with chloroform/CMA in a gradient from 100:0 to 70:30) to provide 1.75 g of 1-(4-chlorobutyl)-2-ethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a light yellow solid.

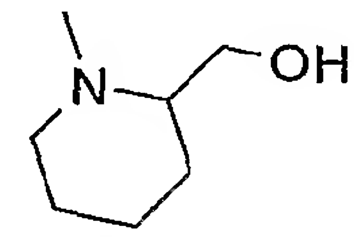
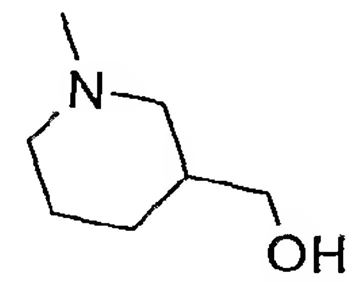
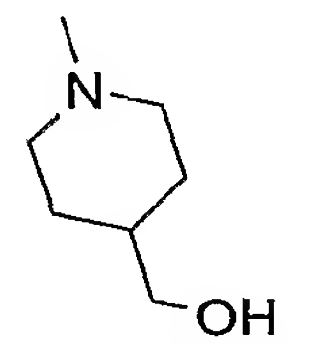
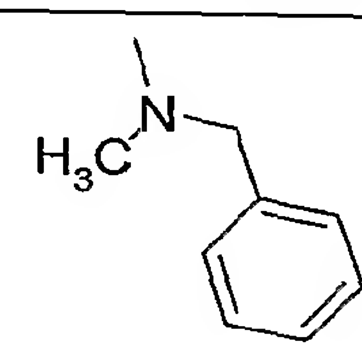
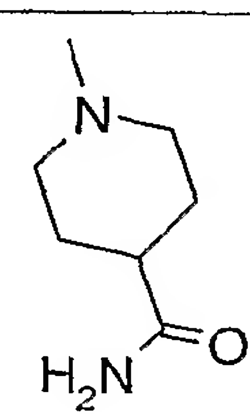
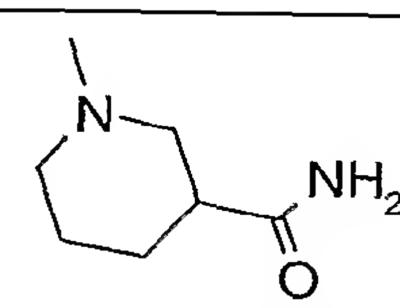
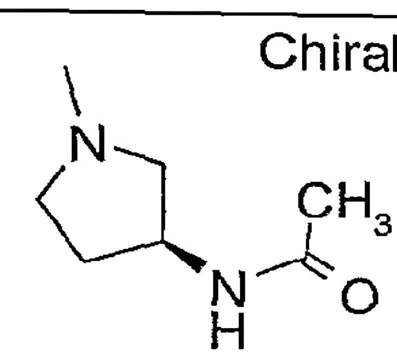
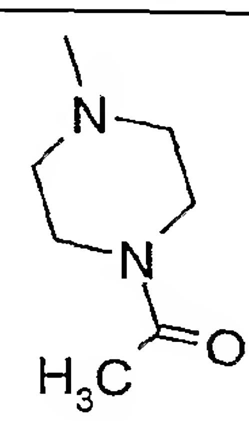
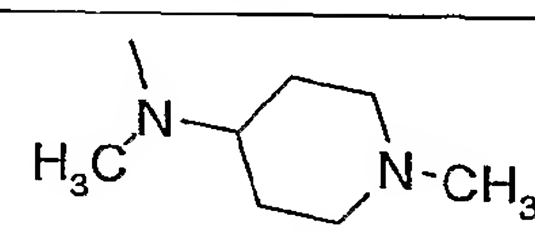
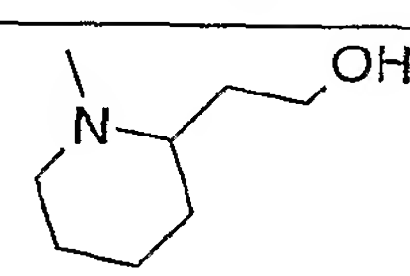
Part B

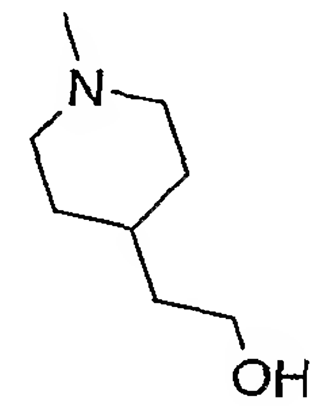
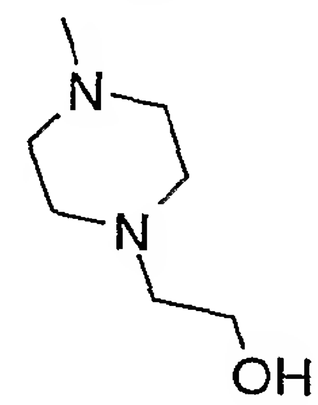
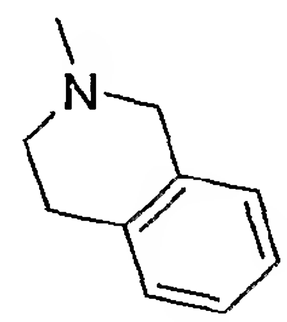
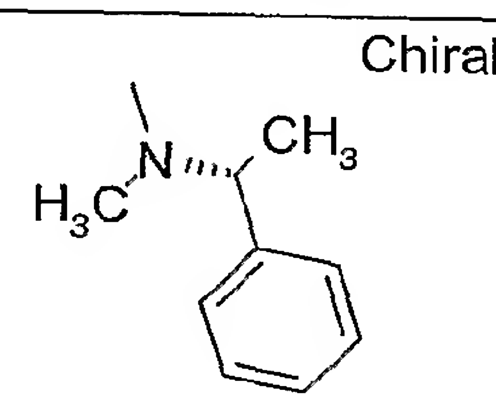
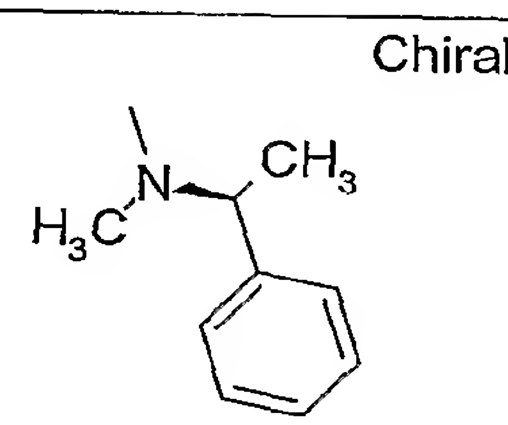
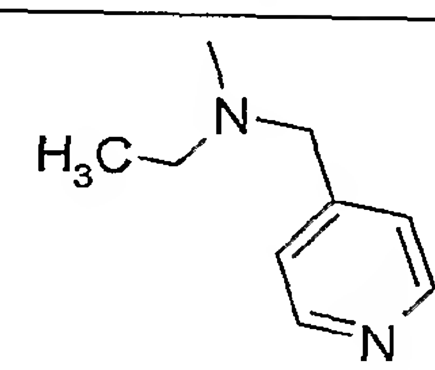
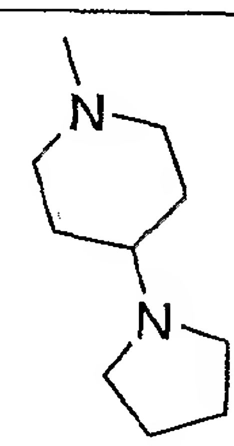
A reagent (0.15 mmol, 1.5 equivalents) from the table below was added to a test tube containing 1-(4-chlorobutyl)-2-ethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (31 mg, 0.10 mmol) and potassium carbonate (approximately 55 mg, 0.40 mmol) in *N,N*-dimethylacetamide (1 mL). The test tubes were capped and heated at 70 °C for approximately 17 hours. The reaction mixtures were filtered and the solvent was removed from the filtrates by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

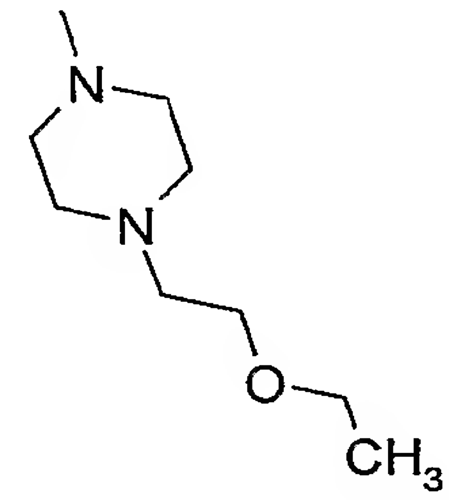
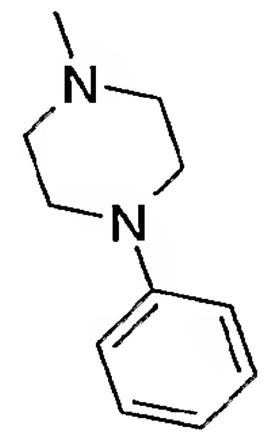
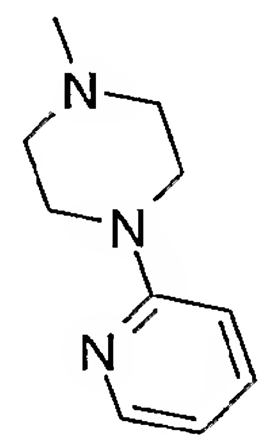
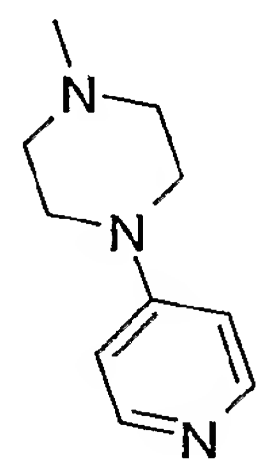
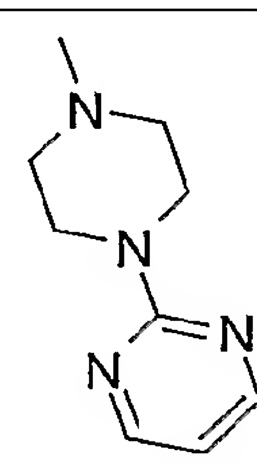
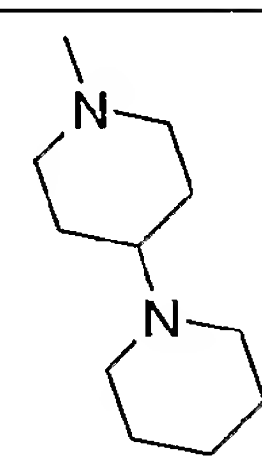


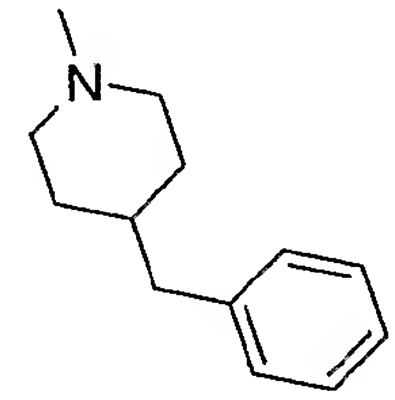
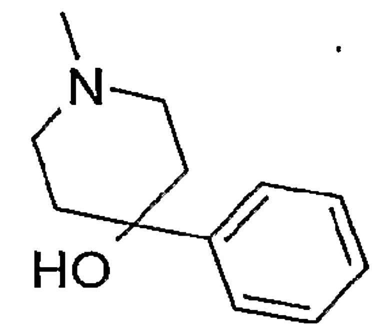
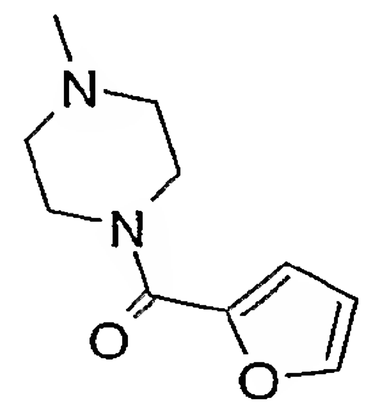
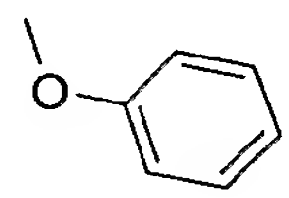
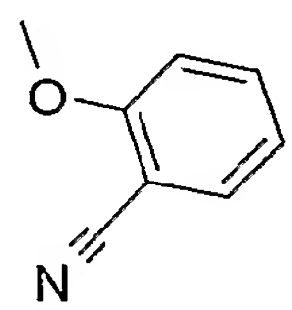
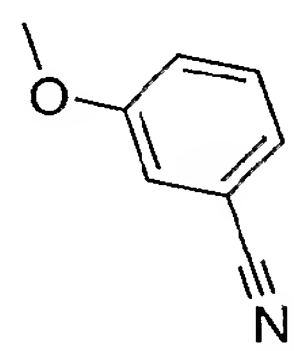
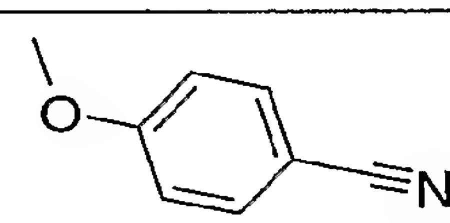
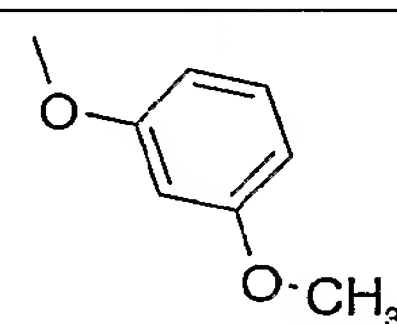
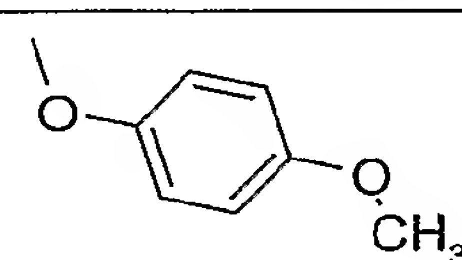
Example	Reagent	R	Measured Mass (M+H)
644	None – starting material	Cl	307.1694

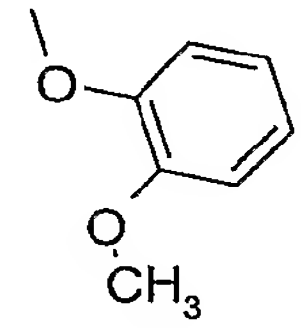
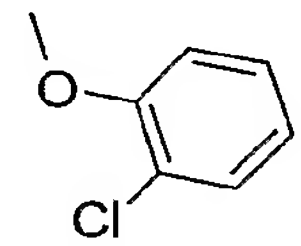
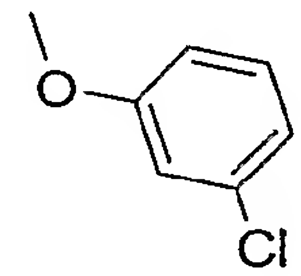
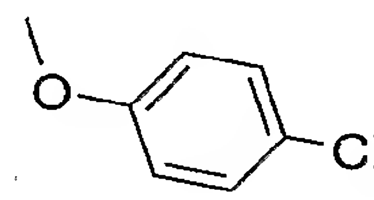
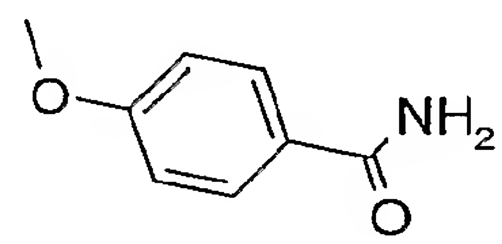
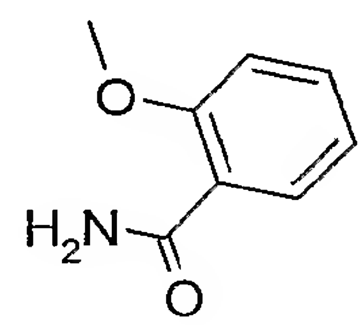
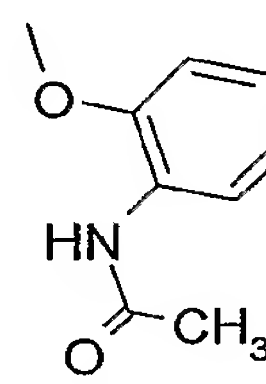
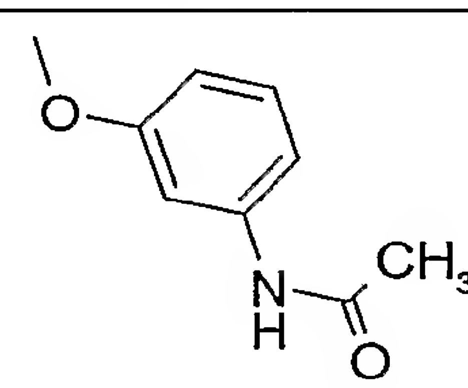
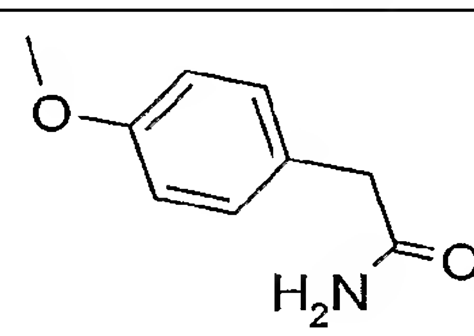
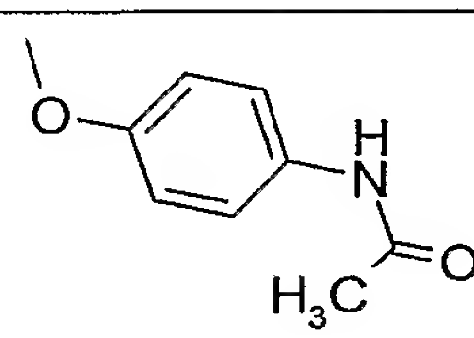
645	Pyrrolidine		342.2682
646	Piperidine		356.2845
647	Morpholine		358.2638
648	Thiazolidine		360.2237
649	1-Methylpiperazine		371.2937
650	4-Hydroxypiperidine		372.2795
651	3-(Dimethylamino)pyrrolidine		385.3103
652	*N,N'*-Dimethyl-3-aminopyrrolidine		385.3098
653	*N*-Ethylpiperazine		385.3092
654	*N*-Methylhomopiperazine		385.3118

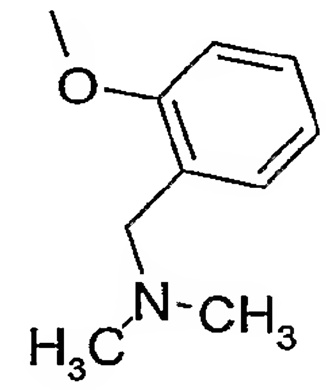
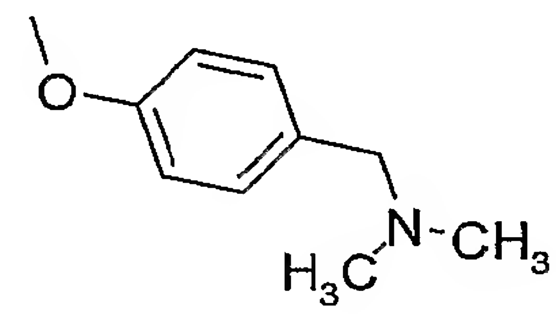
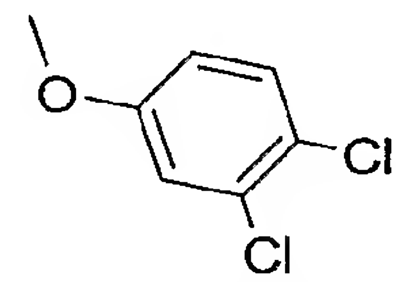
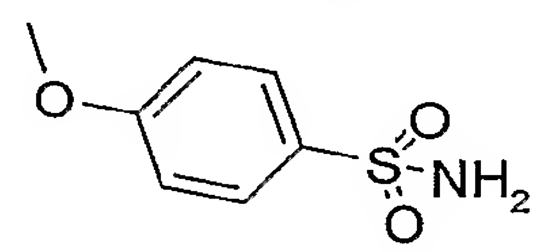
655	2-Piperidinemethanol		386.2896
656	3-(Hydroxymethyl)piperidine		386.2888
657	4-(Hydroxymethyl)piperidine		386.2893
658	*N*-Methylbenzylamine		392.2845
659	Isonipecotamide		399.2902
660	Nipecotamide		399.2894
661	(3S)-(-)-3-Acetamidopyrrolidine		399.2876
662	1-Acetylpiperazine		399.2906
663	1-Methyl-4-(Methylamino)piperidine		399.3218
664	2-Piperidineethanol		400.3098

665	4-Piperidineethanol		400.3116
666	*N*-(2-Hydroxyethyl)piperazine		401.3050
667	1,2,3,4-Tetrahydroisoquinoline		404.2845
668	(R)-(+)-*N*-Methyl-1-Phenylethylamine		406.3002
669	(S)-(-)-*N*-Methyl-1-Phenylethylamine		406.3007
670	4-(Ethylaminomethyl)pyridine		407.2958
671	4-(1-Pyrrolidinyl)-piperidine		425.3405

672	1-(2-Ethoxyethyl)piperazine		429.3372
673	1-Phenylpiperazine		433.3121
674	1-(2-Pyridyl)piperazine		434.3068
675	1-(4-Pyridyl)-piperazine		434.3066
676	1-(2-Pyrimdyl)piperazine		435.3006
677	4-Piperidinopiperidine		439.3589

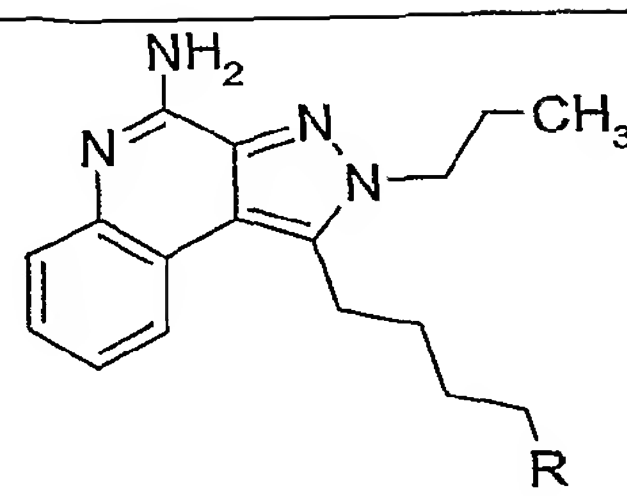
678	4-Benzylpiperidine		446.3323
679	4-Hydroxy-4-phenylpiperidine		448.3083
680	1-(2-Furoyl)piperazine		451.2848
681	Phenol		365.2370
682	2-Cyanophenol		390.2276
683	3-Cyanophenol		390.2332
684	4-Cyanophenol		390.2289
685	3-Methoxyphenol		395.2413
686	4-Methoxyphenol		395.2477

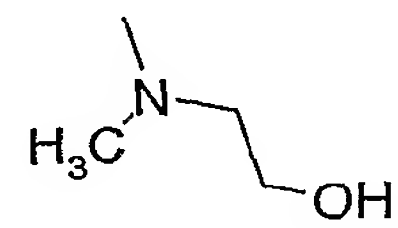
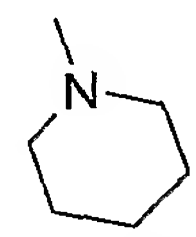
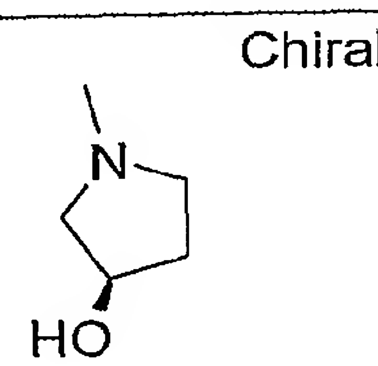
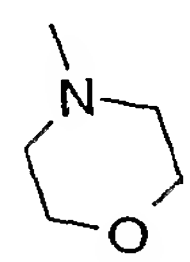
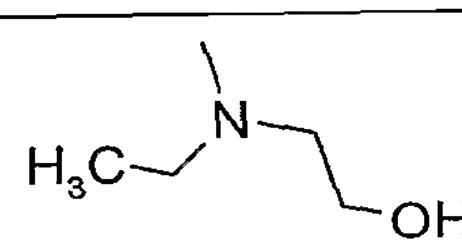
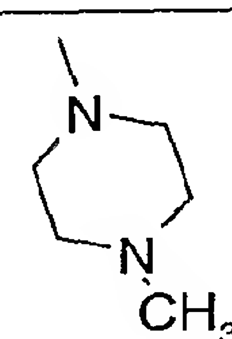
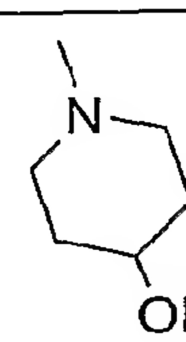
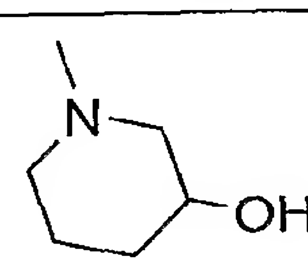
687	Guaiacol		395.2485
688	2-Chlorophenol		399.1955
689	3-Chlorophenol		399.1946
690	4-Chlorophenol		399.1913
691	4-Hydroxybenzamide		408.2427
692	Salicylamide		408.2430
693	2-Acetamidophenol		422.2584
694	3-Acetamidophenol		422.2597
695	4-Hydroxyphenylacetamide		422.2587
696	Acetaminophen		422.2594

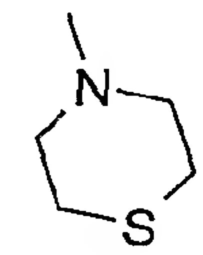
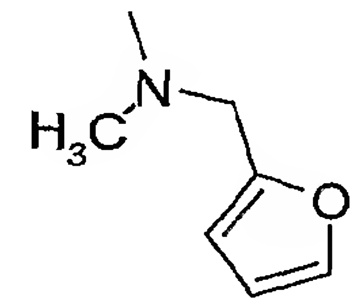
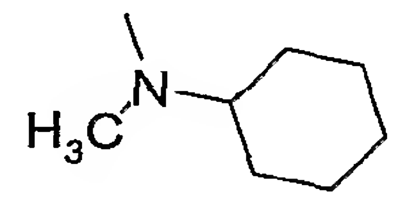
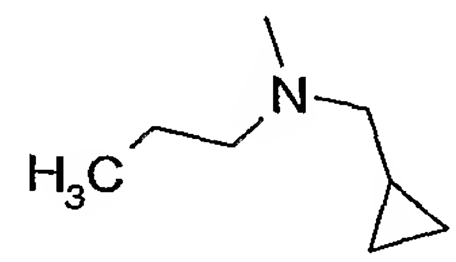
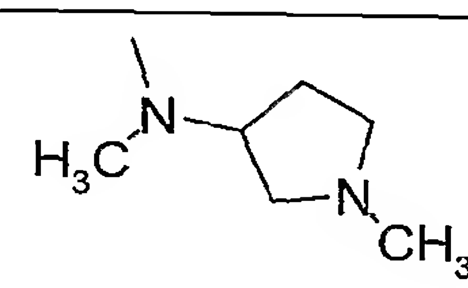
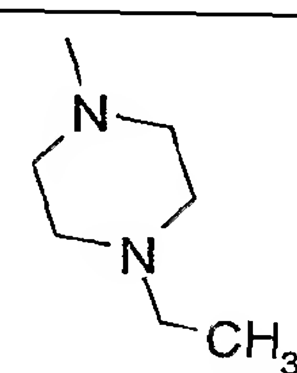
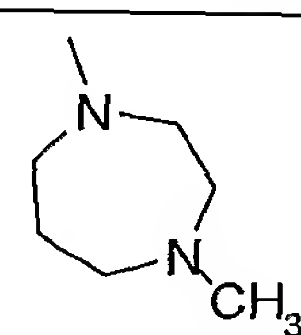
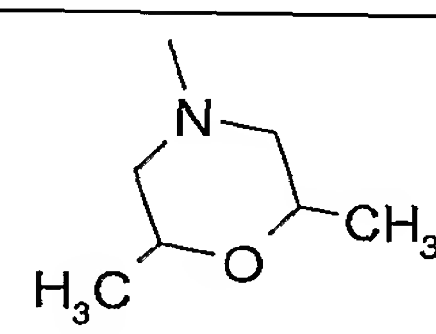
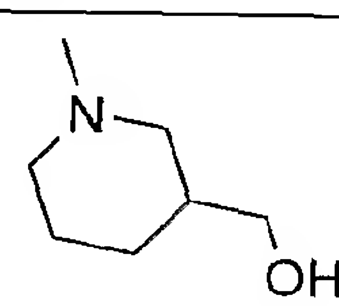
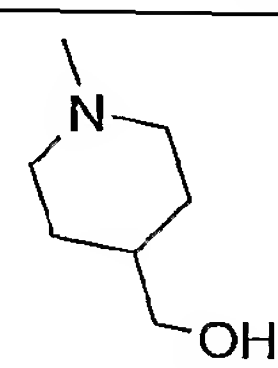
697	2-Dimethylaminomethylphenol		422.2943
698	4-Dimethylaminomethylphenol		422.2960
699	3,4-Dichlorophenol		433.1546
700	4-Hydroxybenzenesulfonamide		444.2099

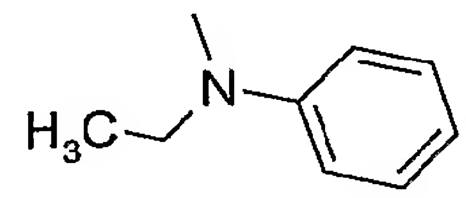
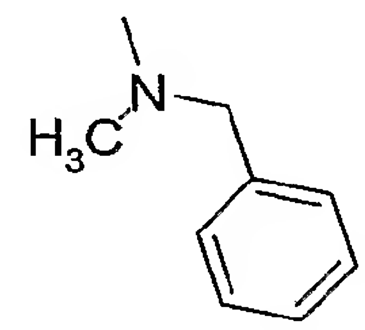
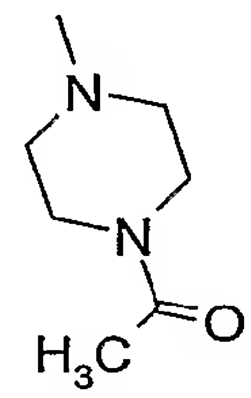
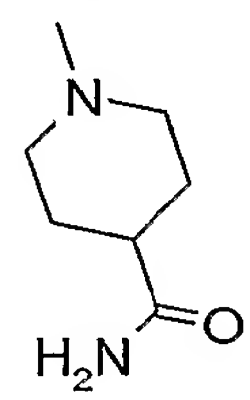
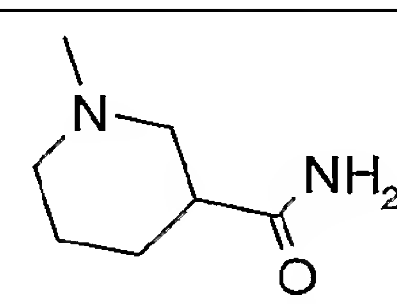
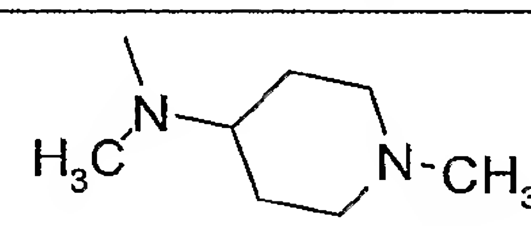
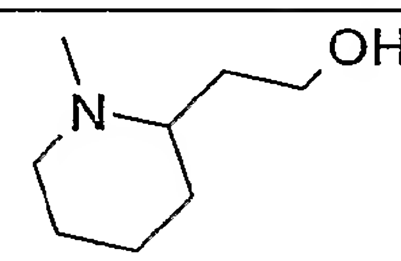
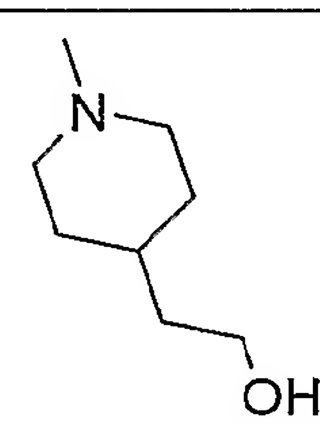
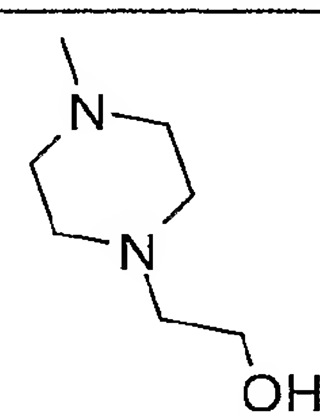
Examples 701 – 775

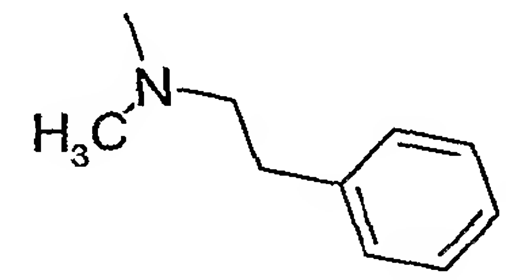
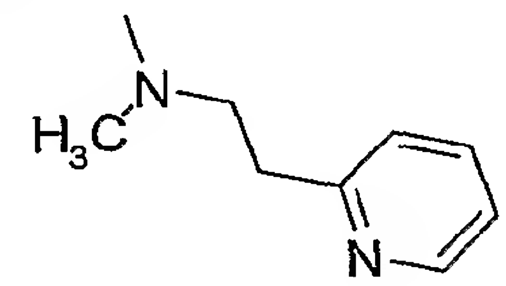
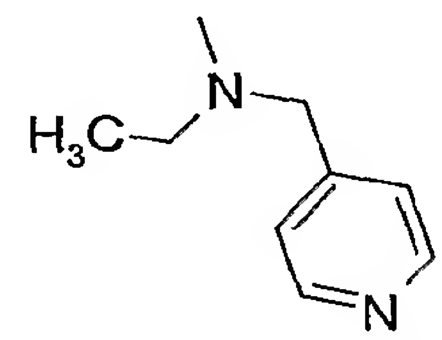
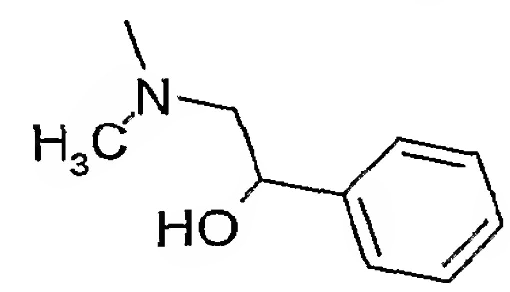
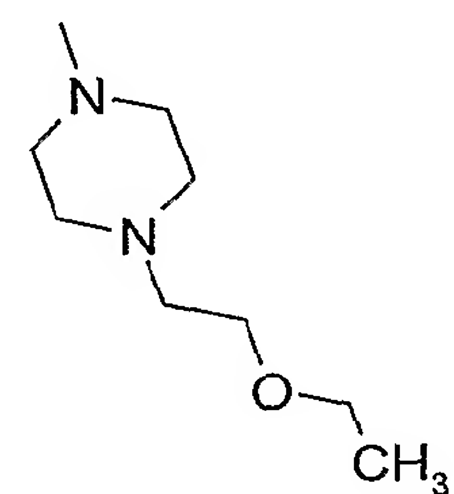
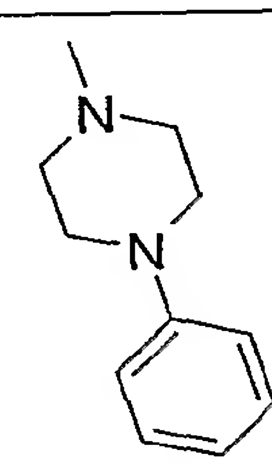
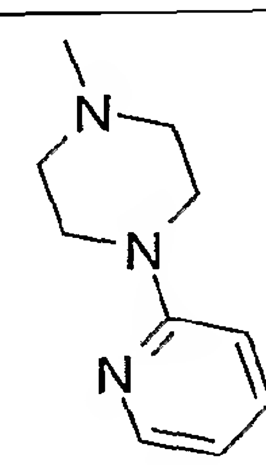
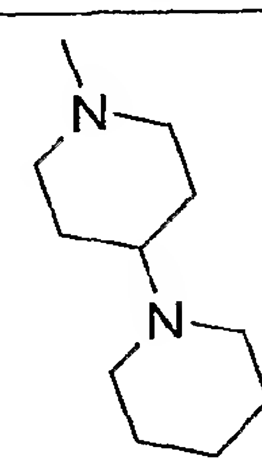
A reagent (0.15 mmol, 1.5 equivalents) from the table below was added to a test tube containing 1-(4-chlorobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine (32 mg, 0.10 mmol, prepared as described in Example 46) and potassium carbonate (approximately 55 mg, 0.40 mmol) in *N,N*-dimethylacetamide (1 mL). The test tubes were capped and heated at 85 °C for approximately 18 hours. The reaction mixtures were filtered and the solvent was removed from the filtrates by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

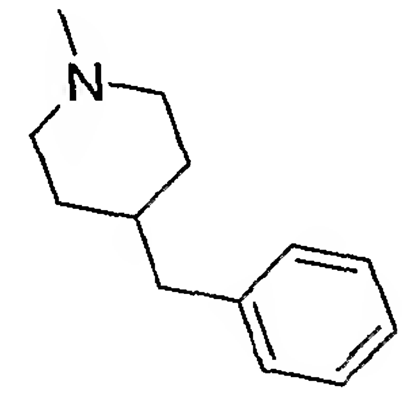
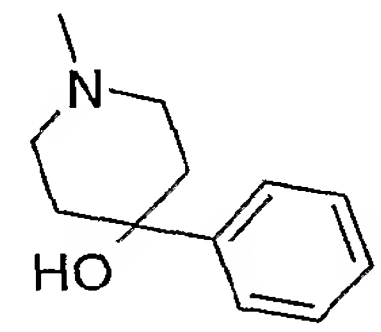
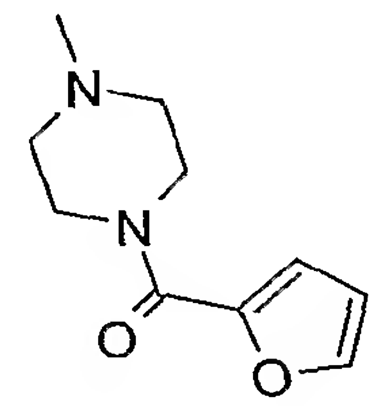
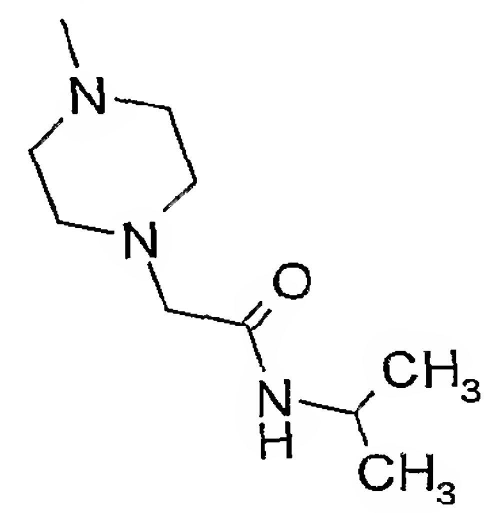
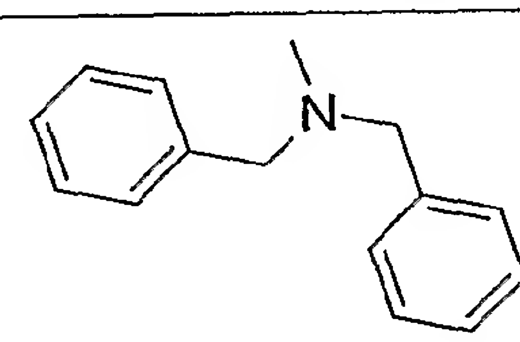
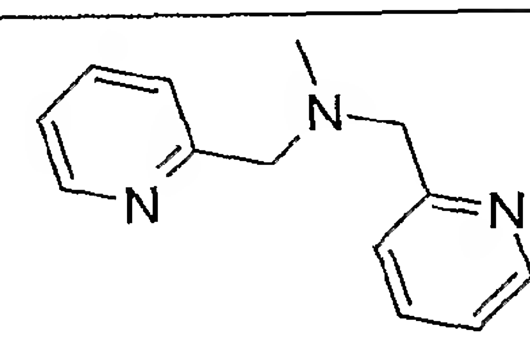
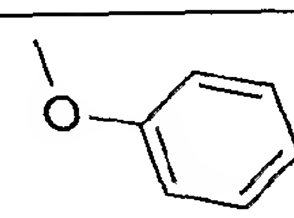
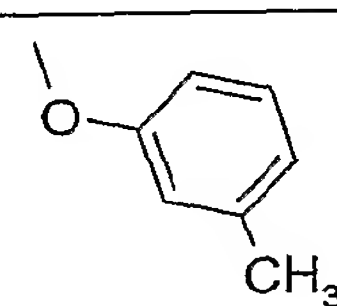
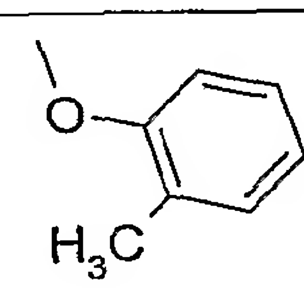


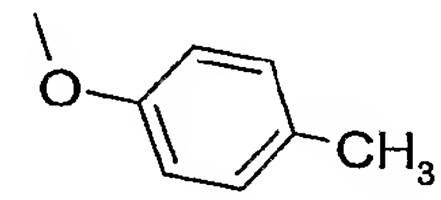
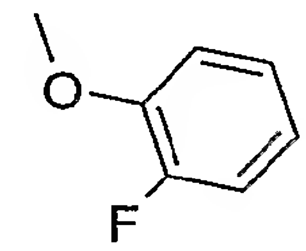
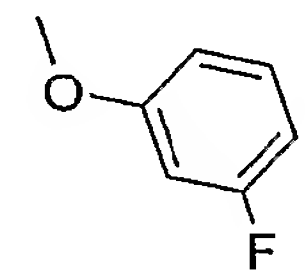
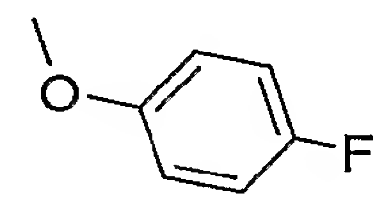
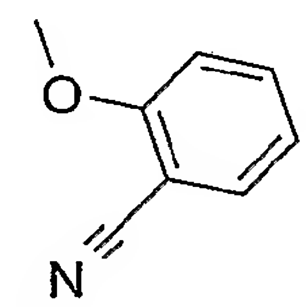
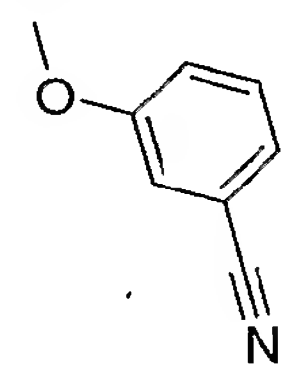
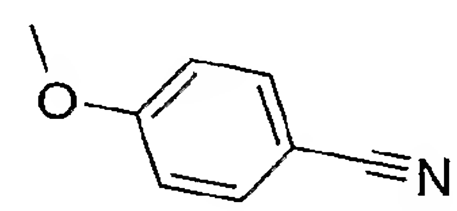
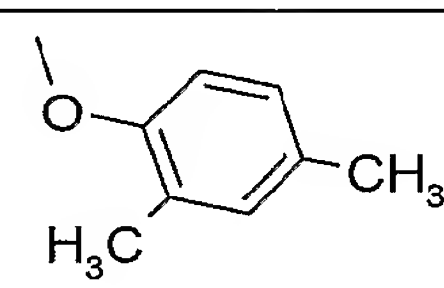
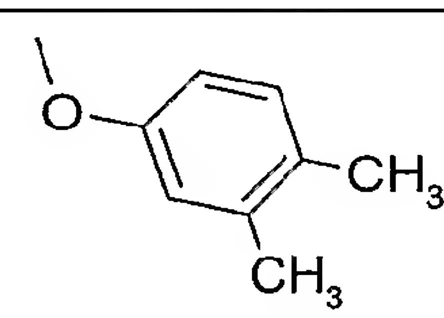
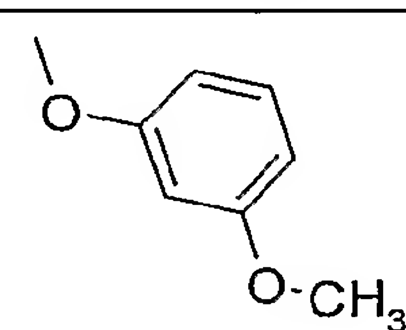
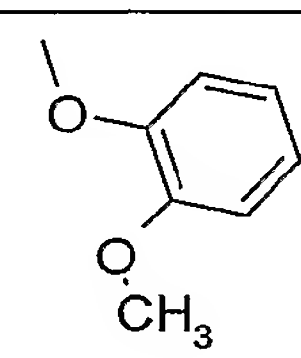
Example	Reagent	R	Measured Mass (M+H)
701	None – starting material		317.1542
702	2-(Methylamino)ethanol		356.2476
703	Piperidine		366.2679
704	(R)-3-Hydroxypyrrolidine		368.2467
705	Morpholine		368.2443
706	2-Ethylaminoethanol		370.2610
707	1-Methylpiperazine		381.2777
708	4-Hydroxypiperidine		382.2585
709	3-Hydroxypiperidine		382.2575

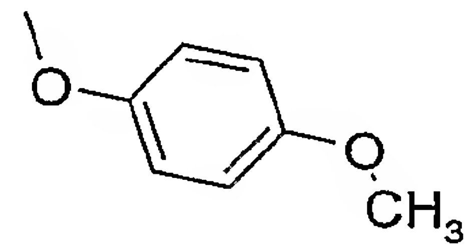
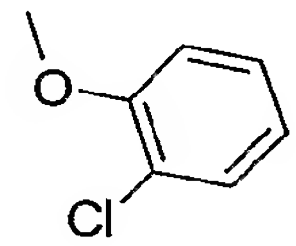
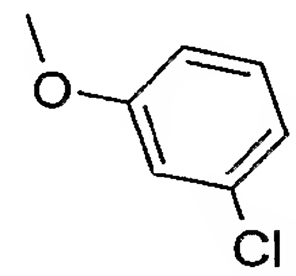
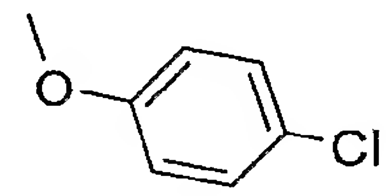
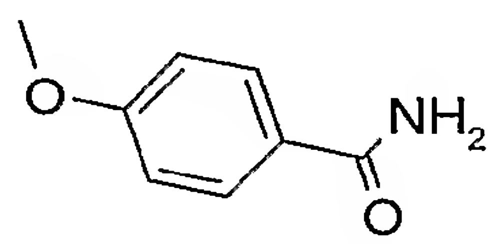
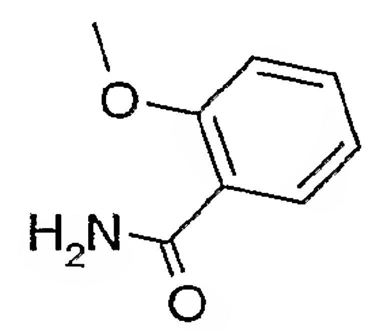
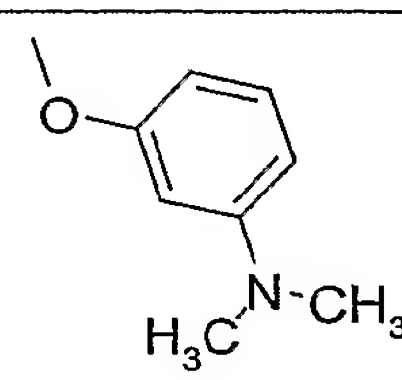
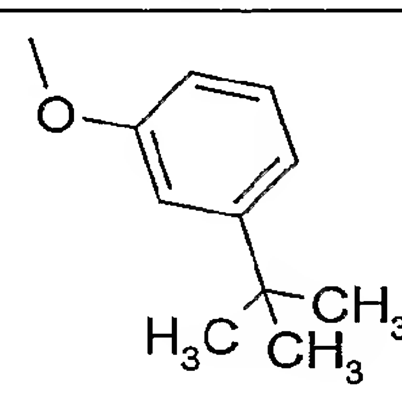
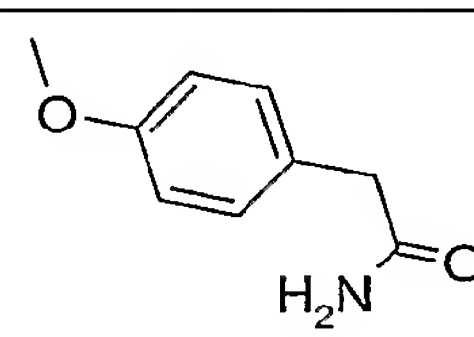
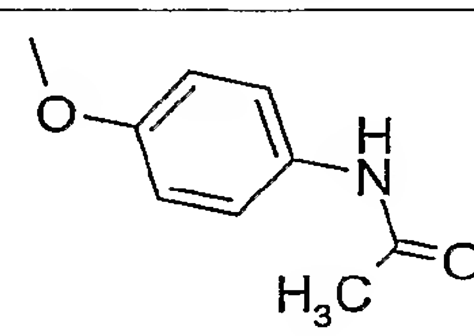
710	Thiomorpholine		384.2242
711	*N*-Methylfurfurylamine		392.2450
712	*N*-Methylcyclohexylamine		394.2995
713	*N*-Propylcyclopropanemethylamine		394.3004
714	*N*,*N'*-Dimethyl-3-aminopyrrolidine		395.2964
715	*N*-Ethylpiperazine		395.2957
716	*N*-Methylhomopiperazine		395.2915
717	2,6-Dimethylmorpholine		396.2796
718	3-(Hydroxymethyl)piperidine		396.2732
719	4-(Hydroxymethyl)piperidine		396.2764

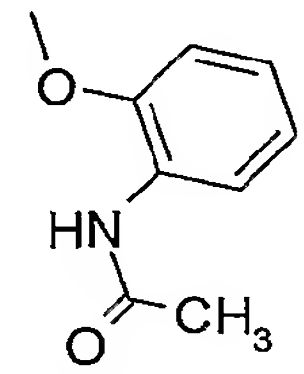
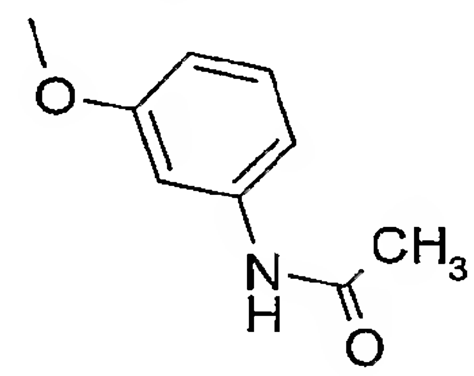
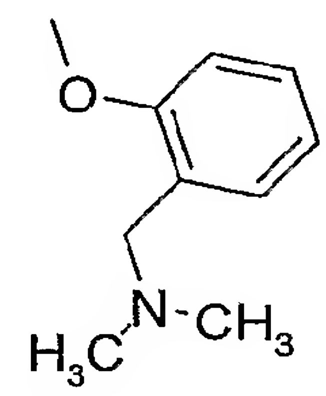
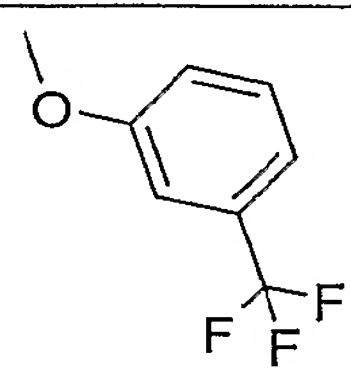
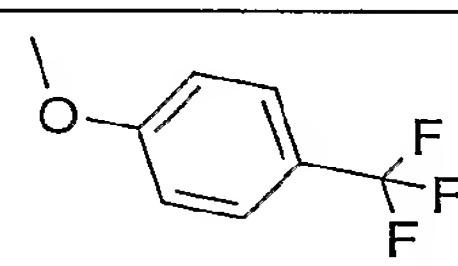
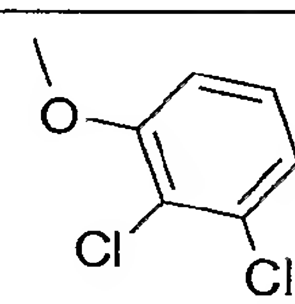
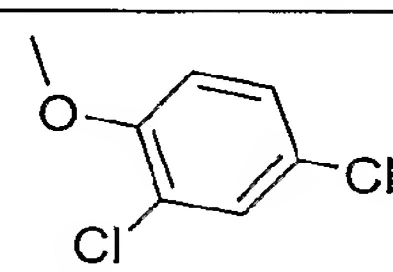
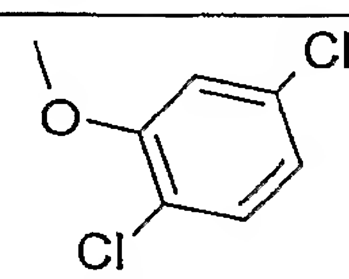
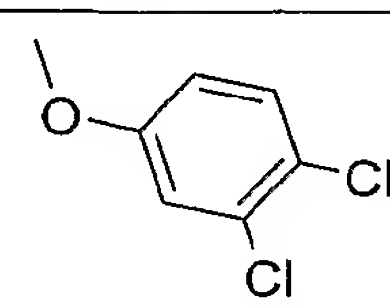
720	*N*-Ethylaniline		402.2686
721	*N*-Methylbenzylamine		402.2680
722	1-Acetylpiperazine		409.2697
723	Isonipecotamide		409.2709
724	Nipecotamide		409.2695
725	1-Methyl-4-(methylamino)piperidine		409.3067
726	2-Piperidineethanol		410.2938
727	4-Piperidineethanol		410.2953
728	*N*-(2-Hydroxyethyl)piperazine		411.2862

729	*N*-Methylphenethylamine		416.2831
730	2-(2-Methylaminoethyl)pyridine		417.2759
731	4-(Ethylaminomethyl)pyridine		417.2796
732	2-Amino-1-phenylethanol		432.2751
733	1-(2-Ethoxyethyl)piperazine		439.3194
734	1-Phenylpiperazine		443.2926
735	1-(2-Pyridyl)piperazine		444.2854
736	4-Piperidinopiperidine		449.3390

737	4-Benzylpiperidine		456.3132
738	4-Hydoxy-4-phenylpiperidine		458.2898
739	1-(2-Furoyl)piperazine		461.2658
740	*N*-Isopropyl-1-piperazineacetamide		466.3321
741	Dibenzylamine		478.3015
742	2,2'-Dipicolylamine		480.2880
743	Phenol		375.2155
744	*m*-Cresol		389.2325
745	*o*-Cresol		389.2318

746	*p*-Cresol		389.2358
747	2-Fluorophenol		393.2096
748	3-Fluorophenol		393.2087
749	4-Fluorophenol		393.2070
750	2-Cyanophenol		400.2164
751	3-Cyanophenol		400.2127
752	4-Cyanophenol		400.2151
753	2,4-Dimethylphenol		403.2482
754	3,4-Dimethylphenol		403.2458
755	3-Methoxyphenol		405.2332
756	2-Methoxyphenol		405.2296

757	4-Methoxyphenol		405.2310
758	2-Chlorophenol		409.1817
759	3-Chlorophenol		409.1787
760	4-Chlorophenol		409.1805
761	4-Hydroxybenzamide		418.2222
762	Salicylamide		418.2272
763	3-Dimethylaminophenol		418.2630
764	3-*tert*-Butylphenol		431.2794
765	4-Hydroxyphenylacetamide		432.2422
766	4-Acetamidophenol		432.2377

767	2-Acetamidophenol		432.2415
768	3-Acetamidophenol		432.2396
769	2-Dimethylaminomethylphenol		432.2734
770	3-Hydroxybenzotrifluoride		443.2042
771	4-Hydroxybenzotrifluoride		443.2050
772	2,3-Dichlorophenol		443.1438
773	2,4-Dichlorophenol		443.1372
774	2,5-Dichlorophenol		443.1427
775	3,4-Dichlorophenol		443.1422

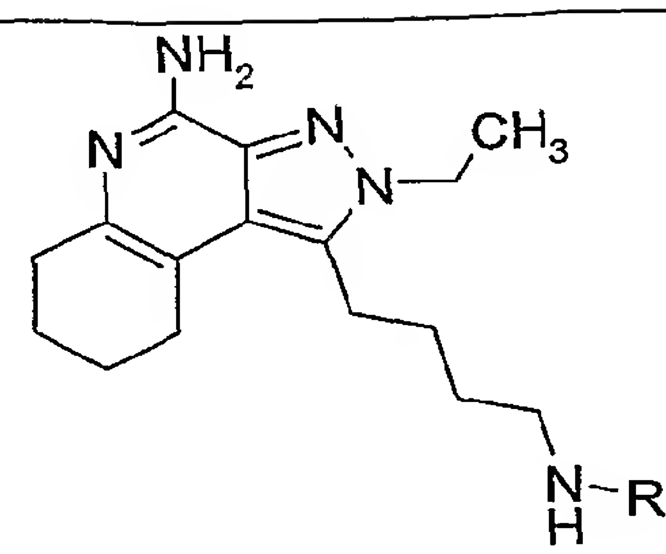
Examples 776 - 799

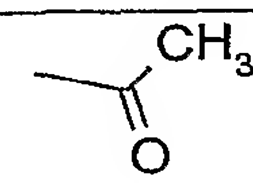
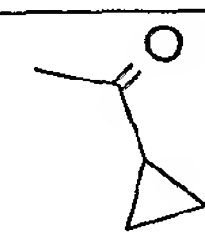
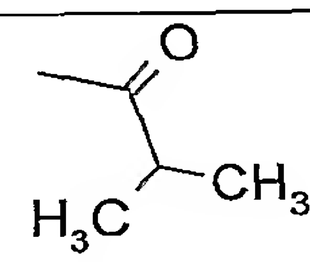
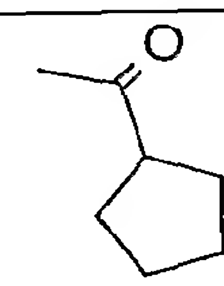
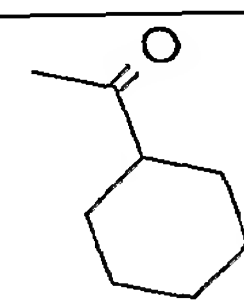
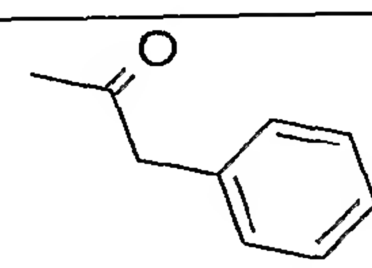
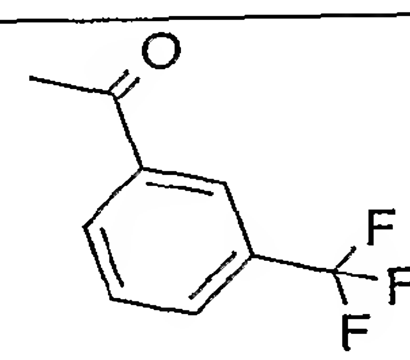
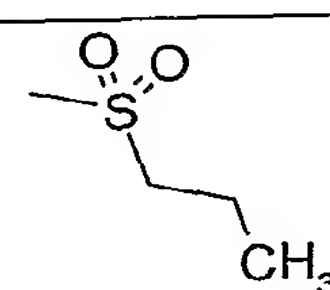
Part A

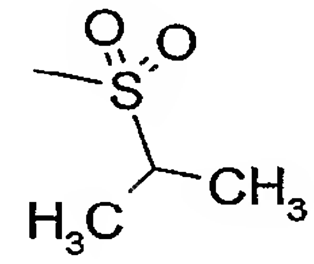
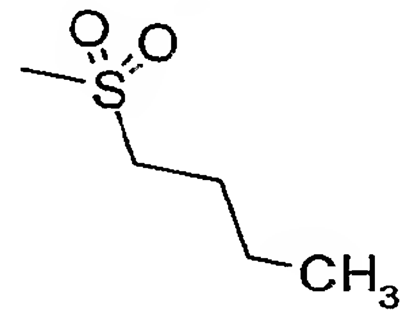
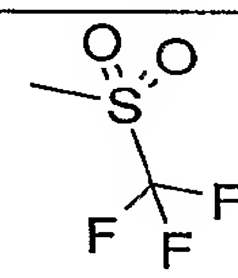
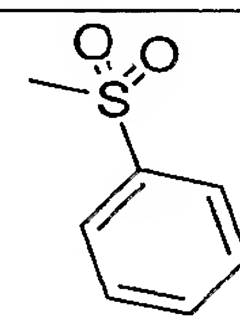
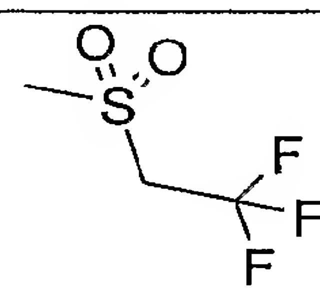
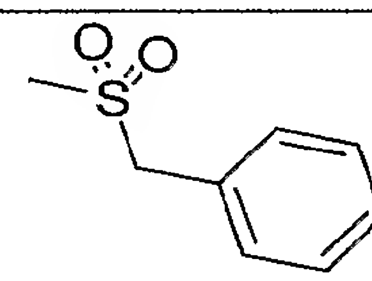
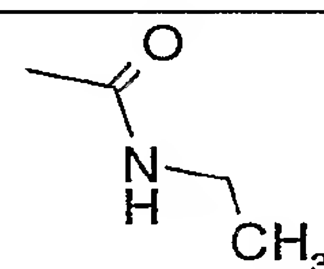
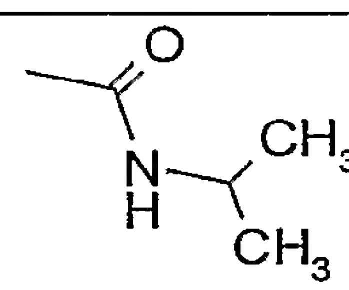
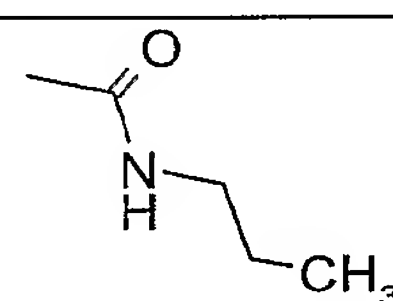
Platinum (IV) oxide (4 g) was added to a solution of 1-(4-aminobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (approximately 24 mmol, prepared as described in Part A of Examples 349-453) in trifluoroacetic acid (80 mL), and the mixture was shaken under hydrogen pressure (50 psi, 3.4 x 10^5 Pa) for two days and subsequently filtered through a layer of CELITE filter agent. The filter cake was washed with methanol, and the filtrate was concentrated under reduced pressure. Water (10 mL) was added, and the resulting solution was adjusted to pH 14 with the addition of 50% aqueous sodium hydroxide. The resulting mixture was extracted with dichloromethane, and the extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 1-(4-aminobutyl)-2-ethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine.

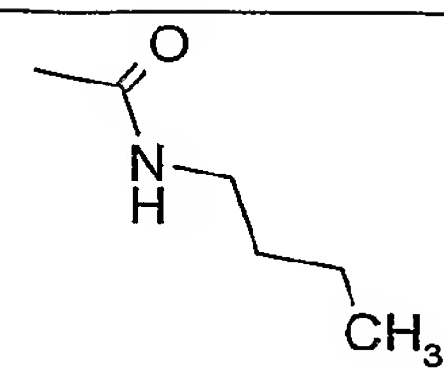
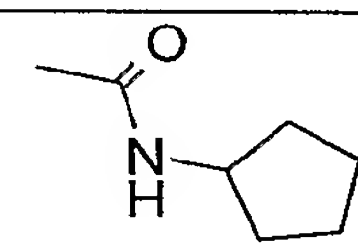
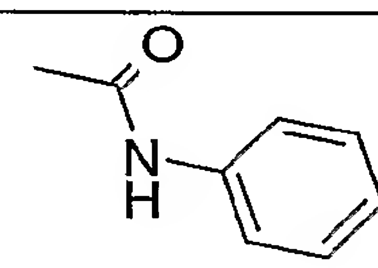
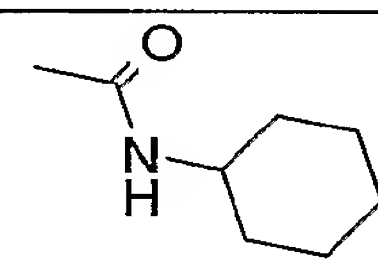
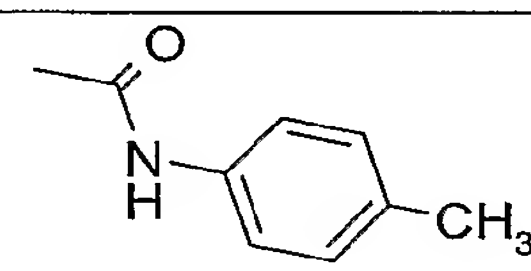
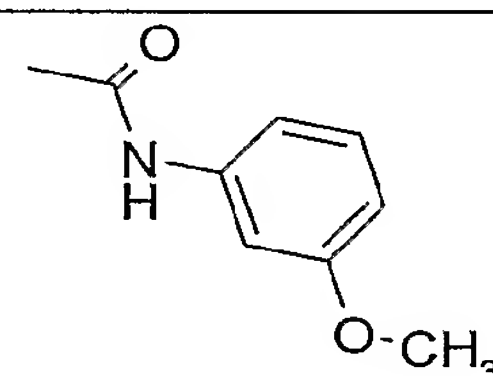
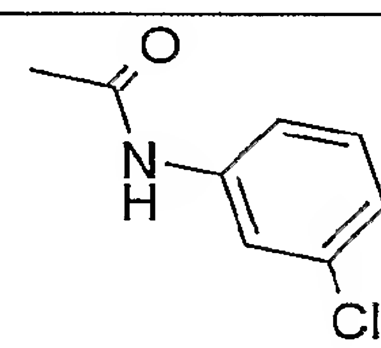
Part B

A reagent (0.048 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(4-aminobutyl)-2-ethyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (12.5 mg, 0.044 mmol) and *N,N*-diisopropylethylamine (approximately 15 µL, 2 equivalents) in chloroform (1 mL). The test tubes were capped and shaken for four hours. Two drops of water were added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
776	Acetyl chloride		330.2275
777	Cyclopropanecarbonyl chloride		356.2417
778	Isobutyryl chloride		358.2600
779	Cyclopentanecarbonyl chloride		384.2771
780	Cyclohexanecarbonyl chloride		398.2882
781	Phenylacetyl chloride		406.2586
782	3-(Trifluoromethyl)benzoyl chloride		460.2296
783	1-Propanesulfonyl chloride		394.2255

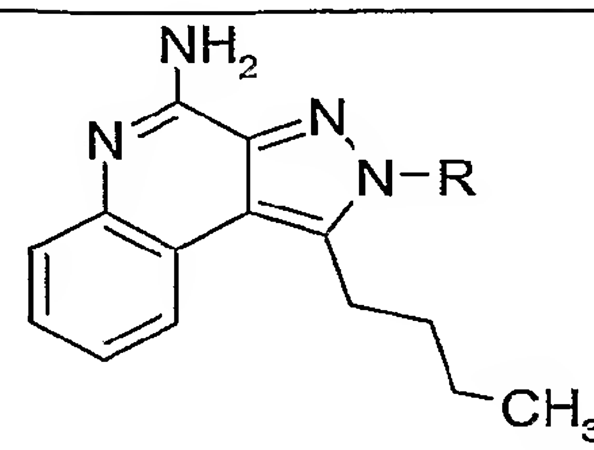
784	Isopropylsulfonyl chloride		394.2260
785	1-Butanesulfonyl chloride		408.2441
786	Trifluoromethanesulfonyl chloride		420.1678
787	Benzenesulfonyl chloride		428.2078
788	2,2,2-Trifluoroethanesulfonyl chloride		434.1819
789	*alpha*-Toluenesulfonyl chloride		442.2266
790	Ethyl isocyanate		359.2540
791	Isopropyl isocyanate		373.2689
792	*N*-Propyl isocyanate		373.2713

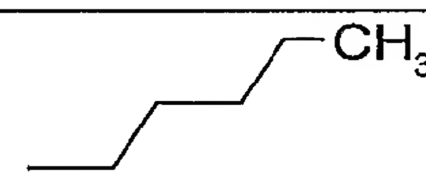
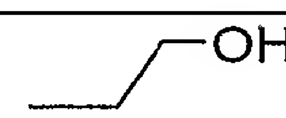
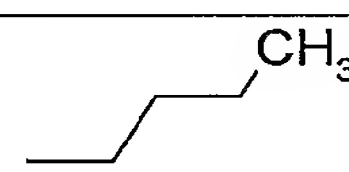
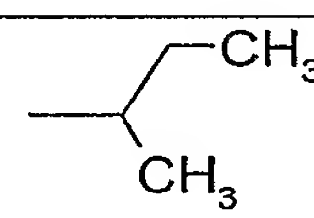
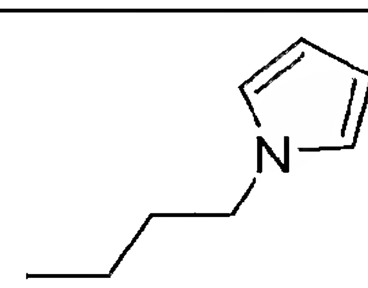
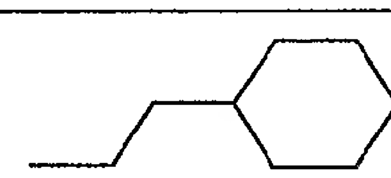
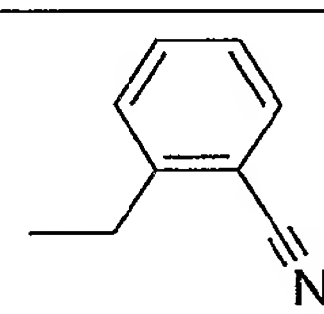
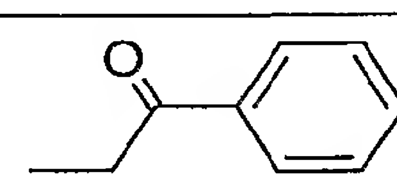
793	*N*-Butyl isocyanate		387.2856
794	Cyclopentyl isocyanate		399.2846
795	Phenyl isocyanate		407.2519
796	Cyclohexyl isocyanate		413.3038
797	*p*-Tolyl isocyanate		421.2720
798	3-Methoxyphenyl isocyanate		437.2661
799	3-Chlorophenyl isocyanate		441.2194

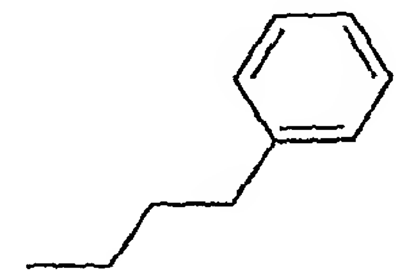
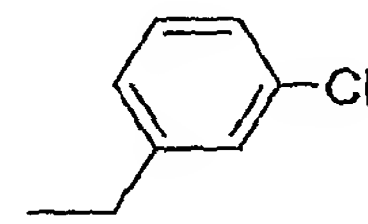
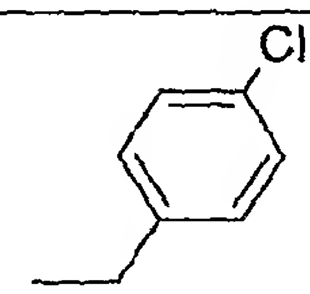
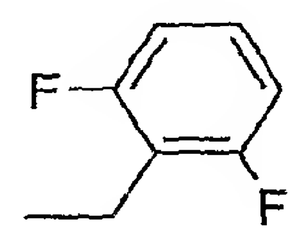
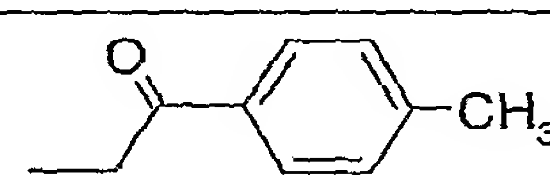
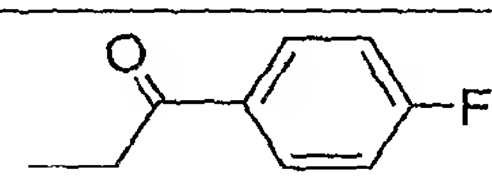
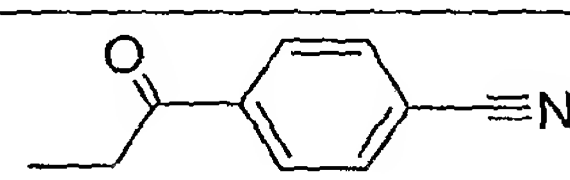
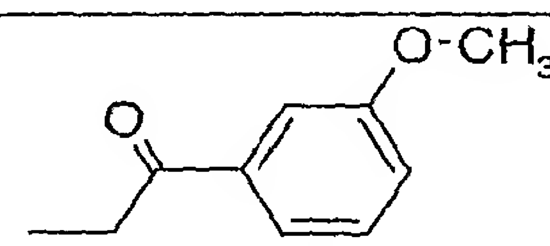
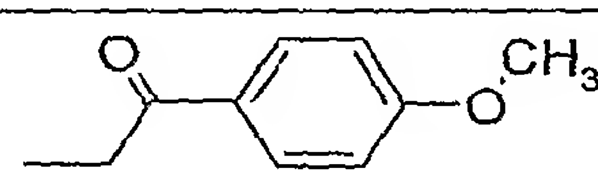
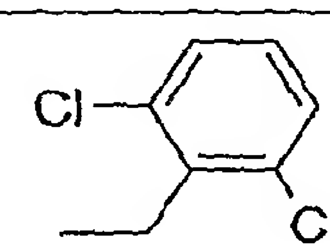
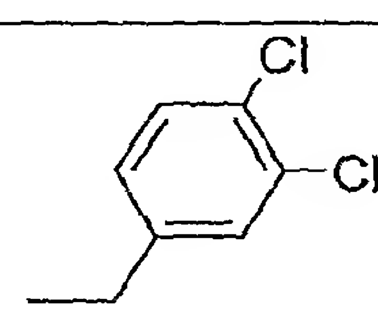
Examples 800 - 819

A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-butyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine hydrochloride (27.6 mg, 0.10 mmol, prepared as described in Part A of Examples 579-581) and potassium carbonate (55 mg, 0.40 mmol) in DMF (1 mL). The test tubes were capped and shaken overnight at ambient temperature. The reaction mixtures were filtered and the solvent was removed from the filtrates by vacuum centrifugation. The compounds were purified as described in

Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

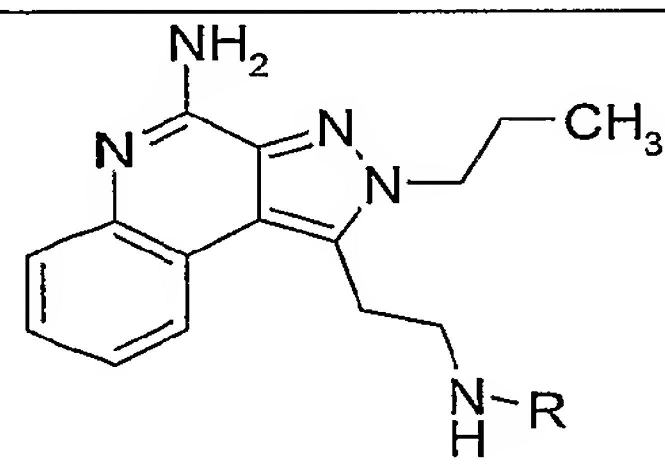


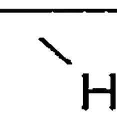
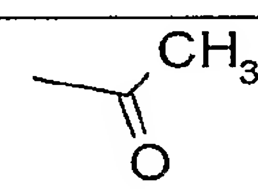
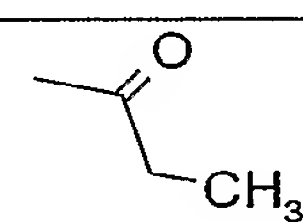
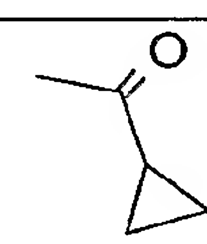
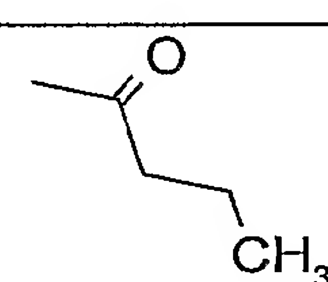
Example	Reagent	R	Measured Mass (M+H)
800	None – starting material	—H	241.1441
801	1-Bromopentane		311.2222
802	2-Iodoethanol		285.1711
803	1-Iodobutane		297.2054
804	2-Iodobutane		297.2053
805	1-(3-Bromopropyl)pyrrole		348.2174
806	2-Cyclohexylethyl bromide		351.2527
807	2-Cyanobenzyl bromide		356.1855
808	2-Bromoacetophenone		359.1871

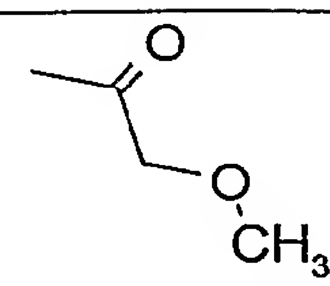
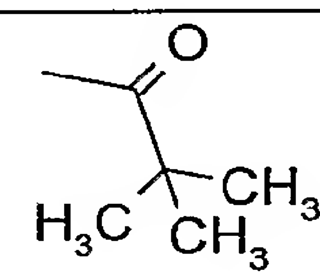
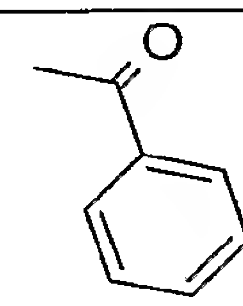
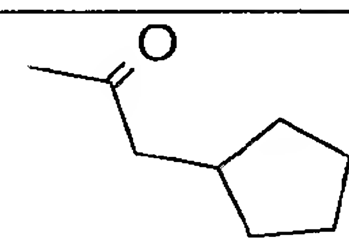
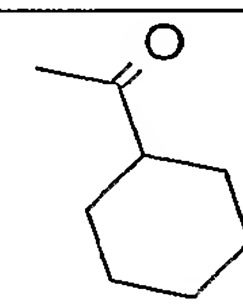
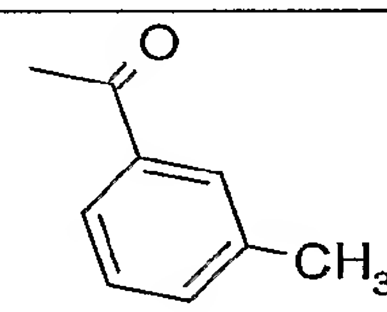
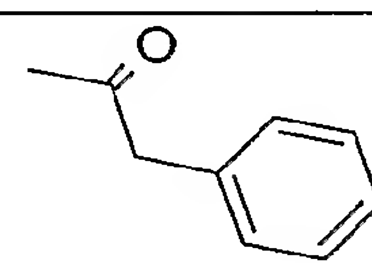
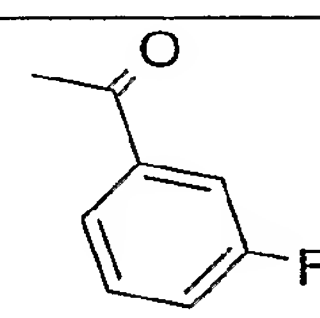
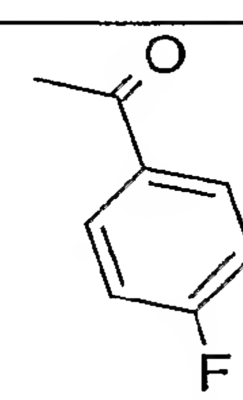
809	1-Bromo-3-Phenylpropane		359.2220
810	3-Chlorobenzyl bromide		365.1521
811	4-Chlorobenzyl bromide		365.1548
812	2,6-Difluorobenzyl bromide		367.1742
813	2-Bromo-4'-methylacetophenone		373.1996
814	2-Bromo-4'-fluoroacetophenone		377.1789
815	4-Cyanophenacyl bromide		384.1801
816	2-Bromo-3'-Methoxyacetophenone		389.2006
817	2-Bromo-4'-Methoxyacetophenone		389.1953
818	2,6-Dichlorobenzyl bromide		399.1115
819	3,4-Dichlorobenzyl bromide		399.1170

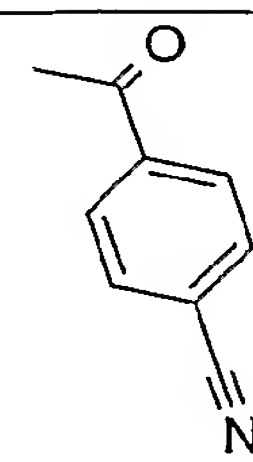
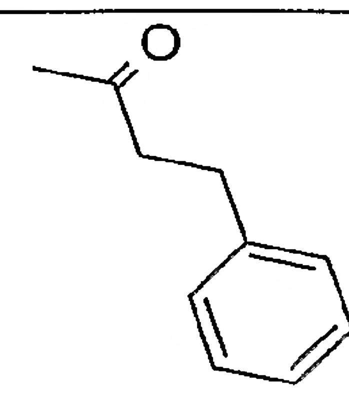
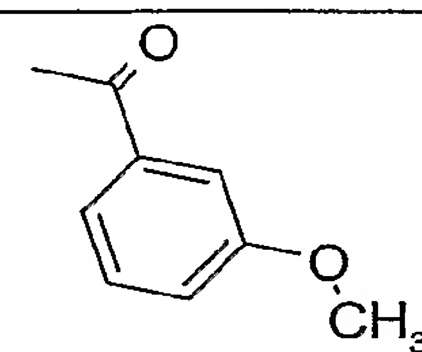
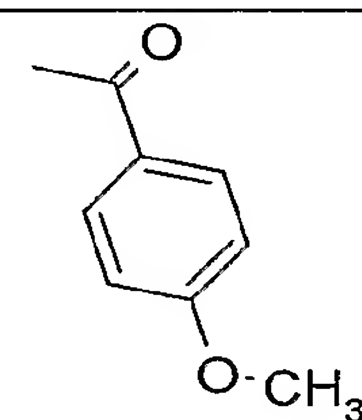
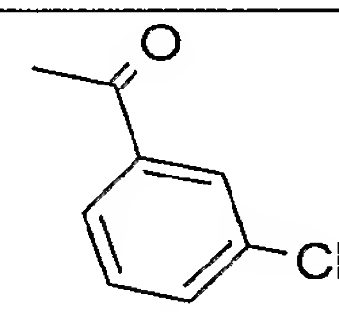
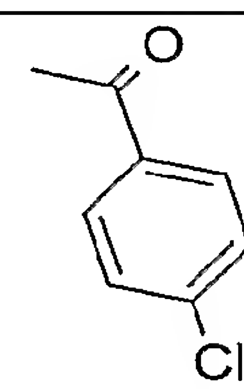
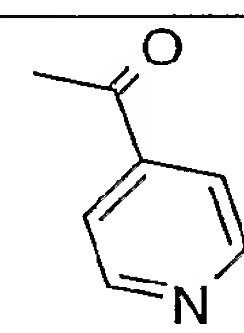
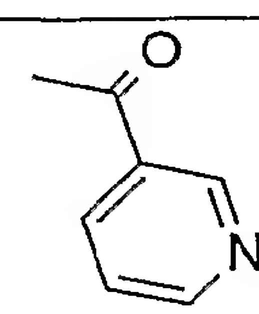
Examples 820 - 904

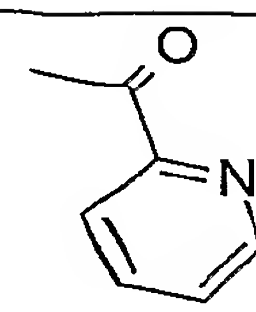
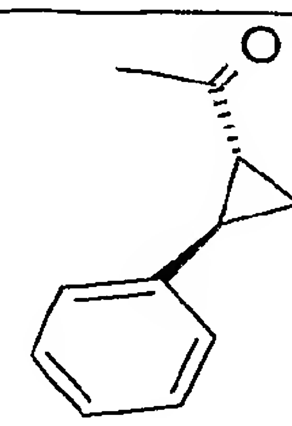
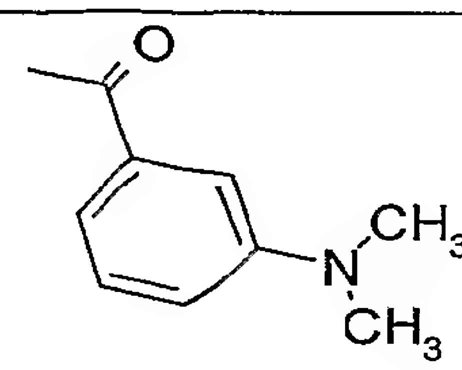
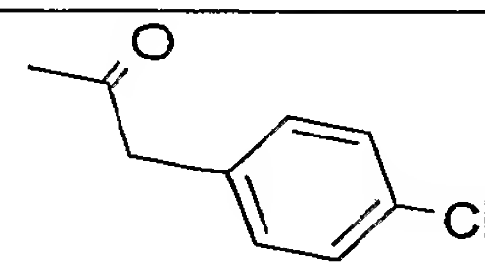
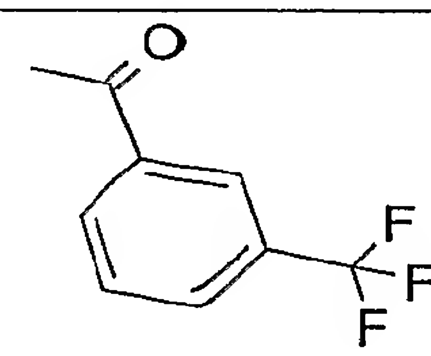
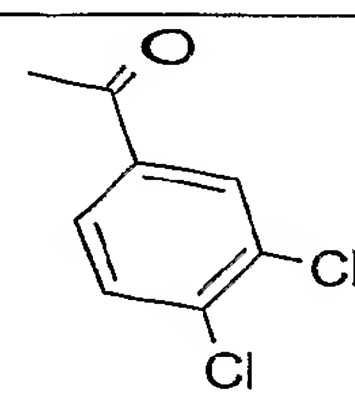
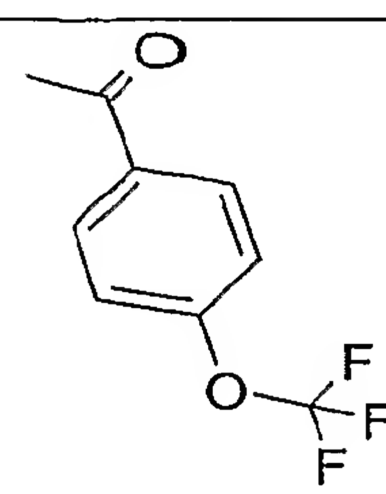
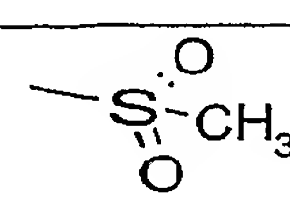
A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(2-aminoethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine dihydrochloride (34 mg, 0.098 mmol, prepared as described in Parts A through H of Example 51) and *N,N*-diisopropylethylamine (approximately 70 µL, 4 equivalents) in chloroform (1 mL). The test tubes were capped and shaken for six hours. Two drops of water were added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

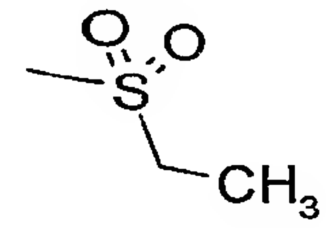
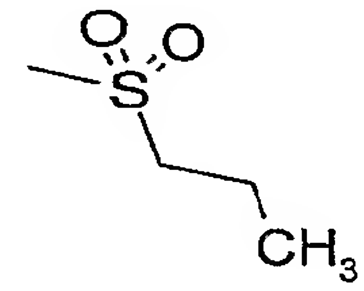
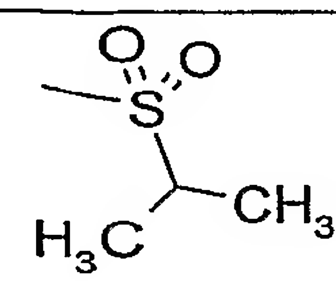
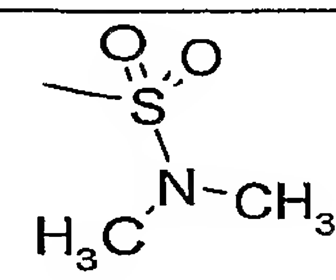
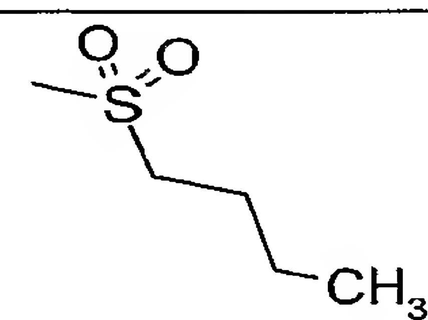
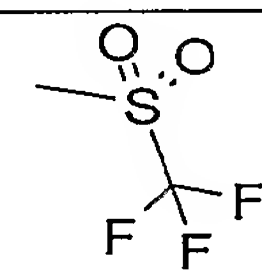
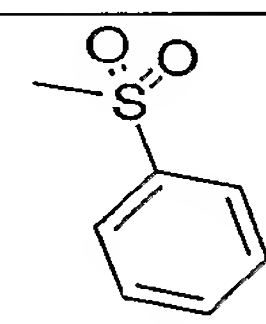
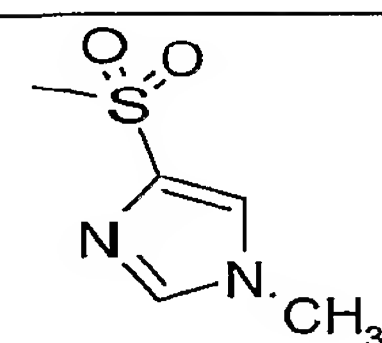
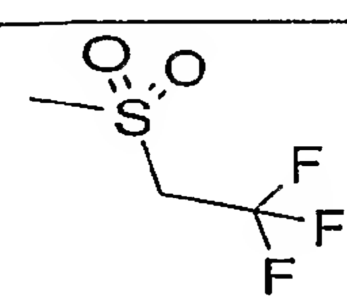


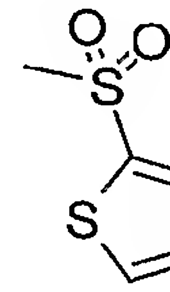
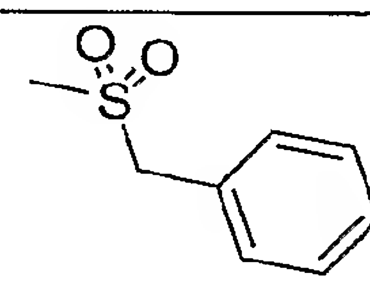
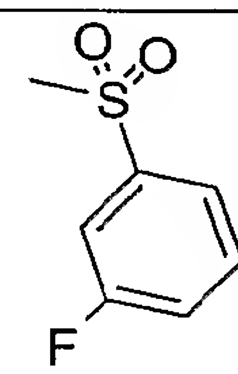
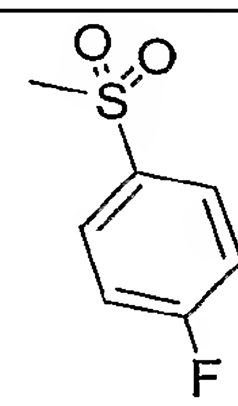
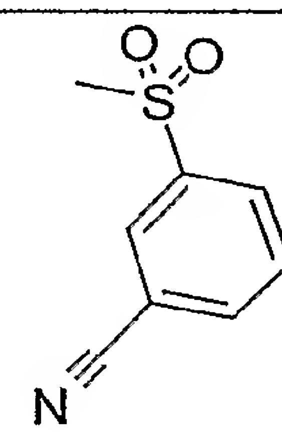
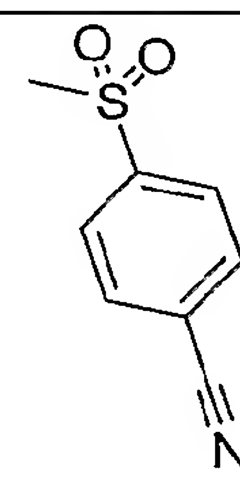
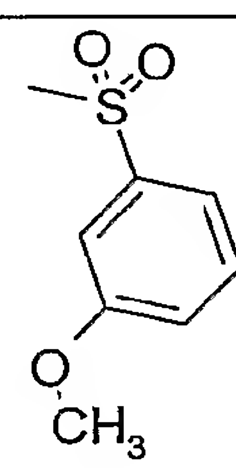
Example	Reagent	R	Measured Mass (M+H)
820	None – starting material		270.1707
821	Acetyl chloride		312.1855
822	Propionyl chloride		326.1965
823	Cyclopropanecarbonyl chloride		338.1994
824	Butyryl chloride		340.2110

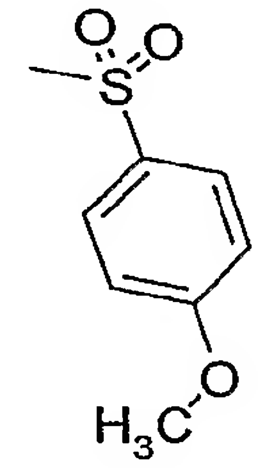
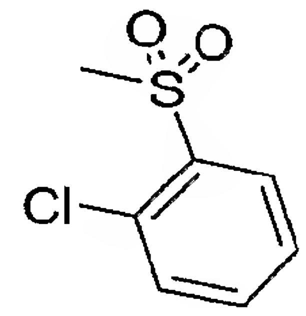
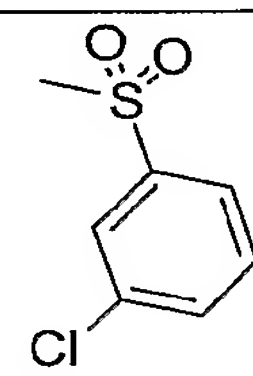
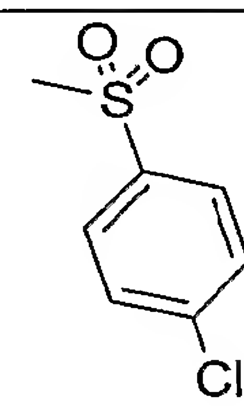
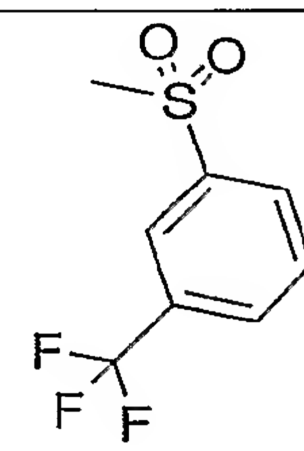
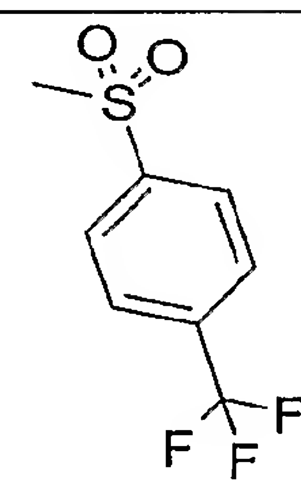
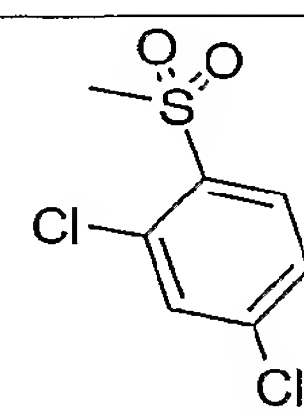
825	Methoxyacetyl chloride		342.1953
826	Pivaloyl chloride		354.2304
827	Benzoyl chloride		374.1986
828	Cyclopentylacetyl chloride		380.2487
829	Cyclohexanecarbonyl chloride		380.2419
830	*m*-Toluoyl chloride		388.2146
831	Phenylacetyl chloride		388.2168
832	3-Fluorobenzoyl chloride		392.1925
833	4-Fluorobenzoyl chloride		392.1896

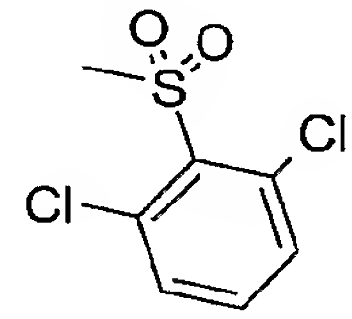
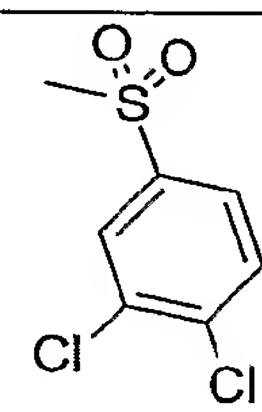
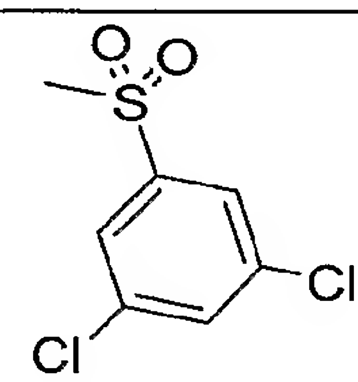
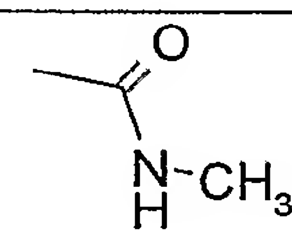
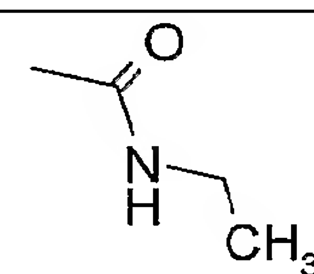
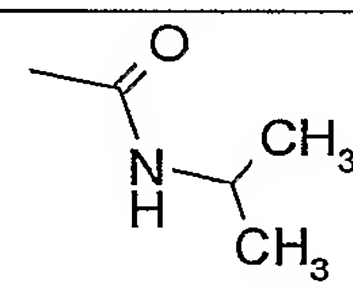
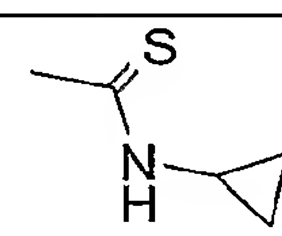
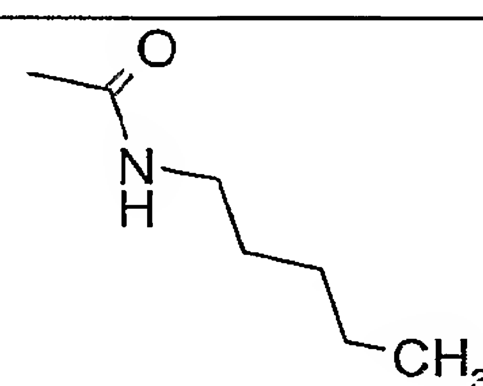
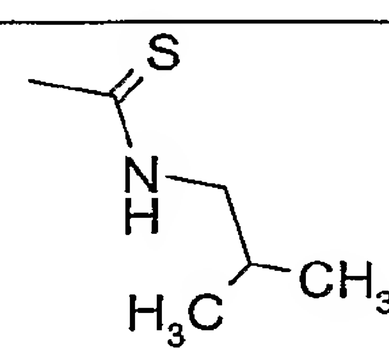
834	4-Cyanobenzoyl chloride		399.1963
835	Hydrocinnamoyl chloride		402.2307
836	3-Methoxybenzoyl chloride		404.2108
837	*p*-Anisoyl chloride		404.2093
838	3-Chlorobenzoyl chloride		408.1565
839	4-Chlorobenzoyl chloride		408.1616
840	Isonicotinoyl chloride hydrochloride		375.1937
841	Nicotinoyl chloride hydrochloride		375.1913

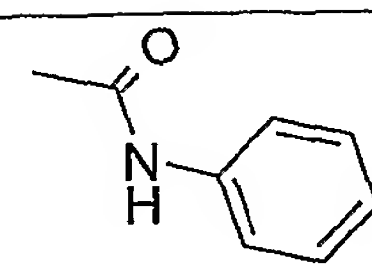
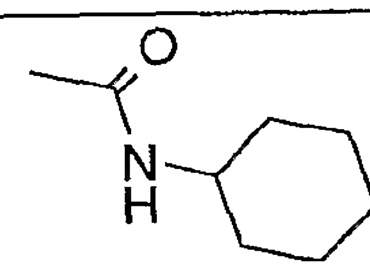
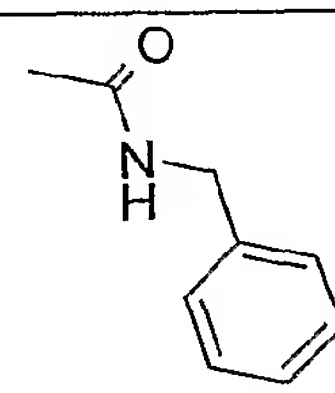
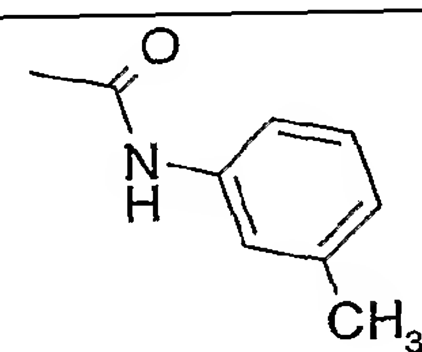
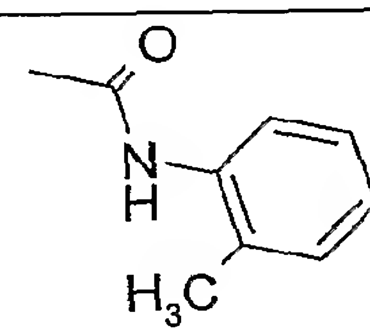
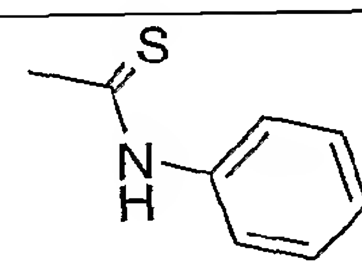
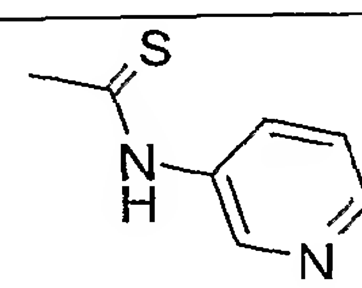
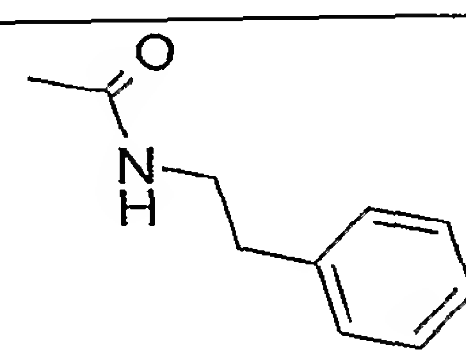
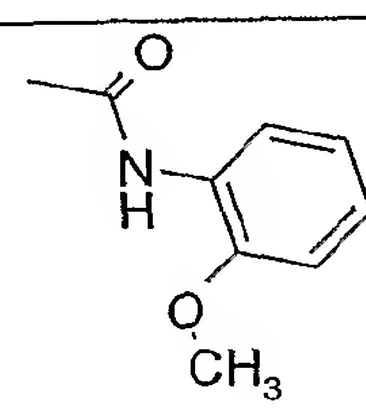
842	Picolinoyl chloride hydrochloride		375.1948
843	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		414.2304
844	3-Dimethylaminobenzoyl chloride		417.2423
845	4-Chlorophenylacetyl chloride		422.1747
846	3-(Trifluoromethyl)benzoyl chloride		442.1840
847	3,4-Dichlorobenzoyl chloride		442.1196
848	4-(Trifluoromethoxy)benzoyl chloride		458.1784
849	Methanesulfonyl chloride		348.1522

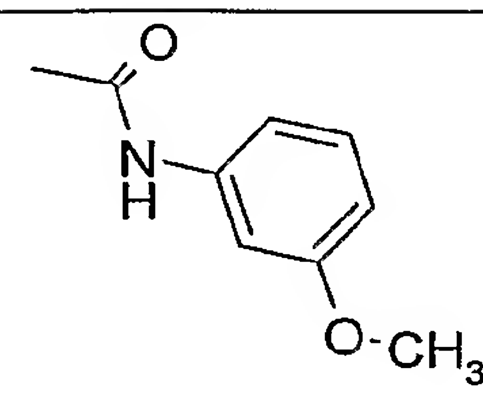
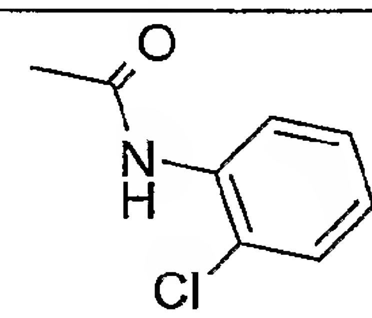
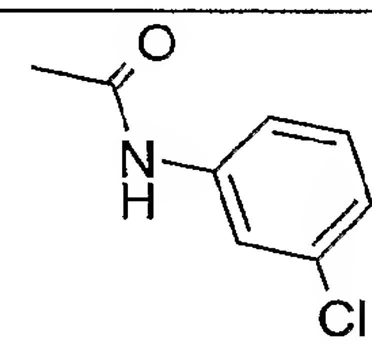
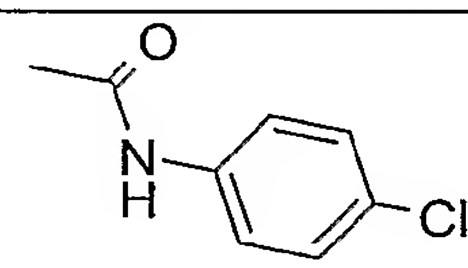
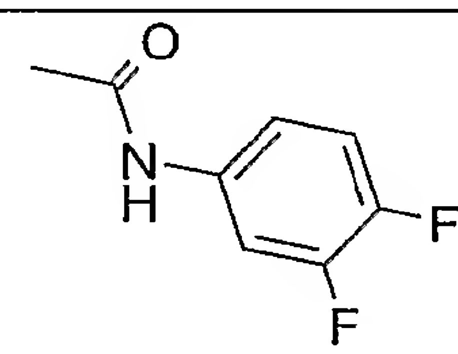
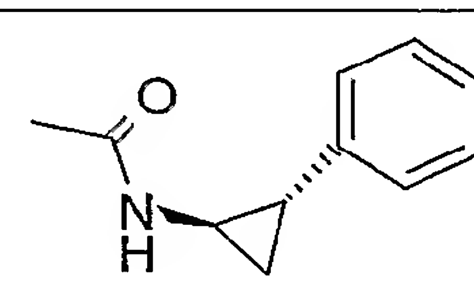
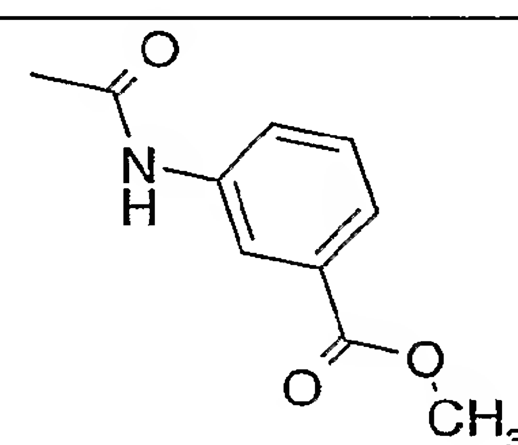
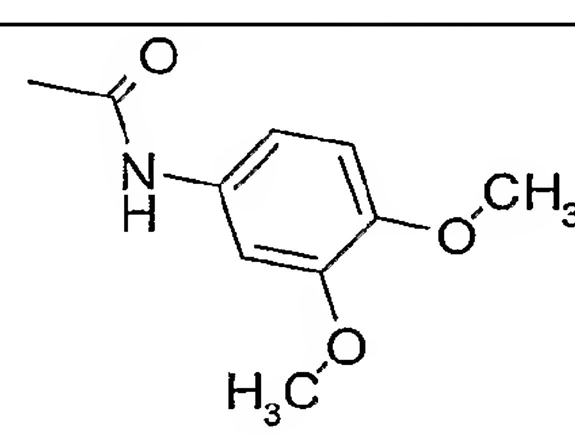
850	Ethanesulfonyl chloride		362.1672
851	1-Propanesulfonyl chloride		376.1812
852	Isopropylsulfonyl chloride		376.1808
853	Dimethylsulfamoyl chloride		377.1767
854	1-Butanesulfonyl chloride		390.2003
855	Trifluoromethanesulfonyl chloride		402.1206
856	Benzenesulfonyl chloride		410.1689
857	1-Methylimidazole-4-sulfonyl chloride		414.1732
858	2,2,2-Trifluoromethanesulfonyl chloride		416.1376

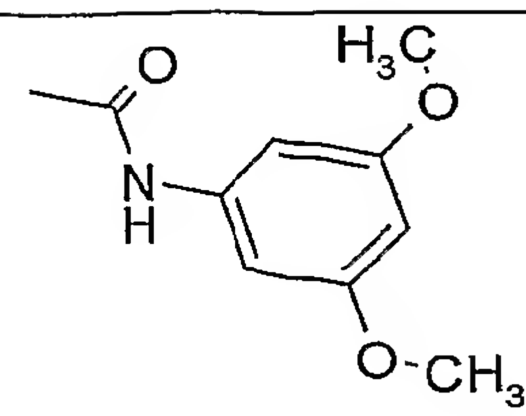
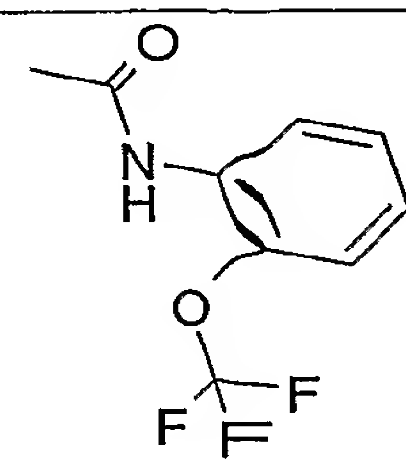
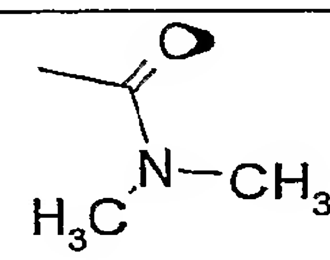
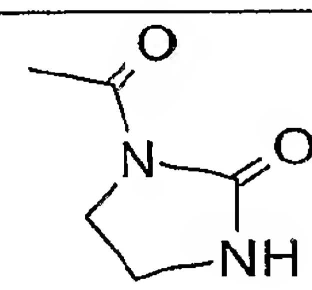
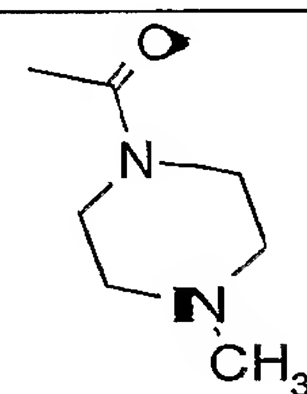
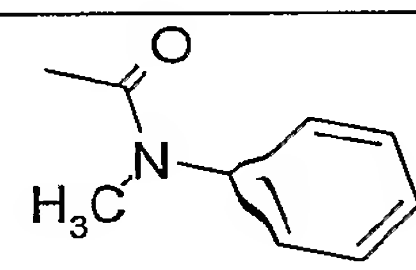
859	2-Thiophenesulfonyl chloride		416.1233
860	*alpha*-Toluenesulfonyl chloride		424.1842
861	3-Fluorobenzenesulfonyl chloride		428.1556
862	4-Fluorobenzenesulfonyl chloride		428.1568
863	3-Cyanobenzenesulfonyl chloride		435.1585
864	4-Cyanobenzenesulfonyl chloride		435.1617
865	3-Methoxybenzenesulfonyl chloride		440.1798

866	4-Methoxybenzenesulfonyl chloride		440.1721
867	2-Chlorobenzenesulfonyl chloride		444.1277
868	3-Chlorobenzenesulfonyl chloride		444.1272
869	4-Chlorobenzenesulfonyl chloride		444.1278
870	3-(Trifluoromethyl)benzenesulfonyl chloride		478.1482
871	4-(Trifluoromethyl)benzenesulfonyl chloride		478.1519
872	2,4-Dichlorobenzenesulfonyl chloride		478.0887

873	2,6-Dichlorobenzenesulfonyl chloride		478.0858
874	3,4-Dichlorobenzenesulfonyl chloride		478.0838
875	3,5-Dichlorobenzenesulfonyl chloride		478.0890
876	Methyl isocyanate		327.1915
877	Ethyl isocyanate		341.2110
878	Isopropyl isocyanate		355.2263
879	Cyclopropyl isothiocyanate		369.1870
880	Pentyl isocyanate		383.2596
881	Isobutyl isothiocyanate		385.2207

882	Phenyl isocyanate		389.2116
883	Cyclohexyl isocyanate		395.2597
884	Benzyl isocyanate		403.2283
885	*m*-Tolyl isocyanate		403.2268
886	*o*-Tolyl isocyanate		403.2238
887	Phenyl isothiocyanate		405.1867
888	3-Pyridyl isothiocyanate		406.1828
889	2-Phenethyl isocyanate		417.2416
890	2-Methoxyphenyl isocyanate		419.2187

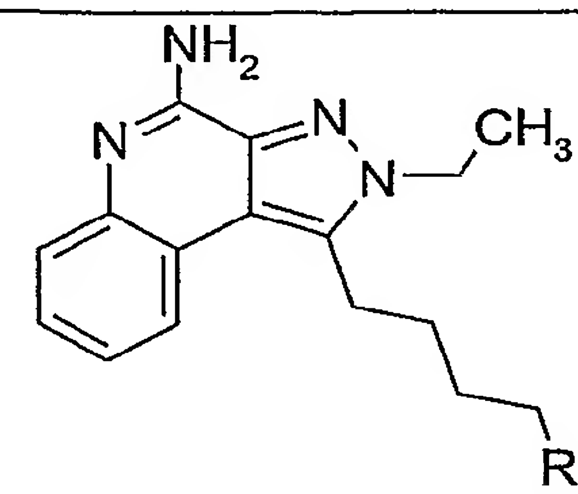
891	3-Methoxyphenyl isocyanate		419.2167
892	2-Chlorophenyl isocyanate		423.1716
893	3-Chlorophenyl isocyanate		423.1736
894	4-Chlorophenyl isocyanate		423.1716
895	3,4-Difluorophenyl isocyanate		425.1877
896	*trans*-2-Phenylcyclopropyl isocyanate		429.2428
897	3-Carbomethoxyphenyl isocyanate		447.2178
898	3,4-Dimethoxyphenyl isocyanate		449.2318

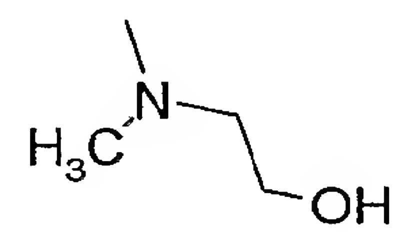
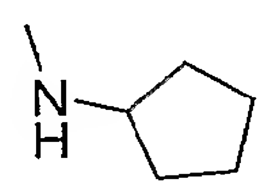
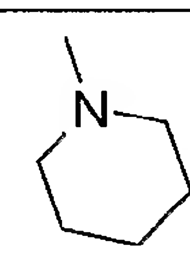
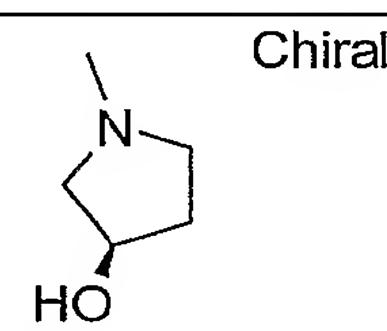
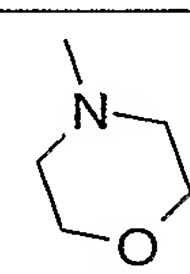
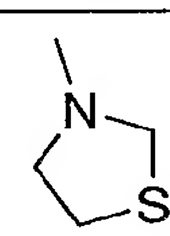
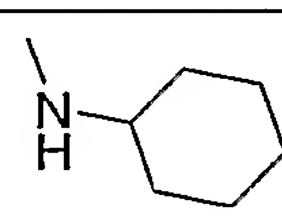
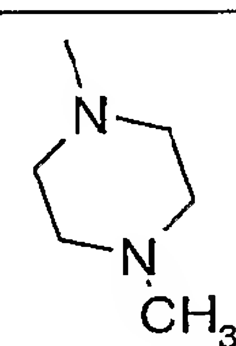
899	3,5-Dimethoxylphenyl isocyanate		449.2270
900	2-(Trifluoromethoxy)phenyl isocyanate		473.1876
901	*N,N*-Dimethylcarbamoyl chloride		341.2104
902	2-Oxo-1-imidazolidinecarbonyl chloride		382.1967
903	4-Methyl-1-piperazinecarbonyl chloride		396.2530
904	*N*-Methyl-*N*-Phenylcarbamoyl chloride		403.2245

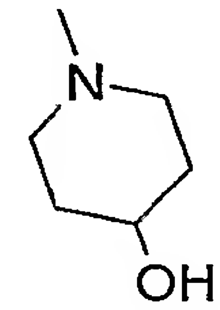
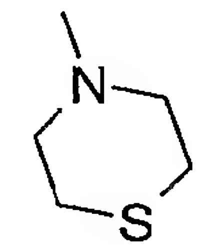
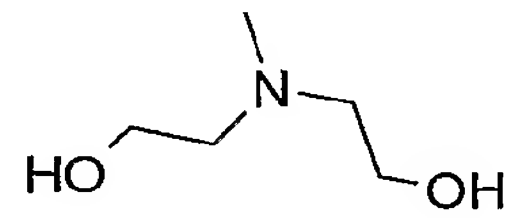
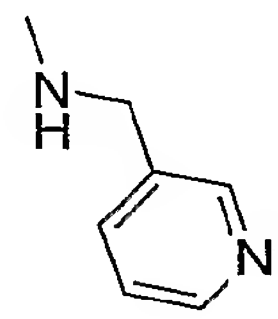
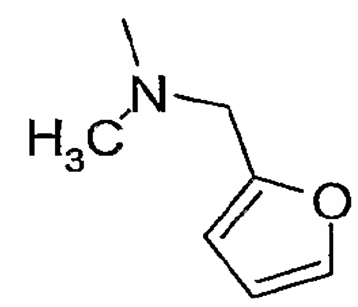
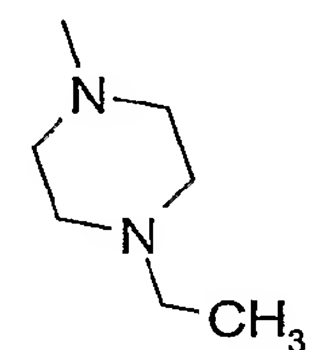
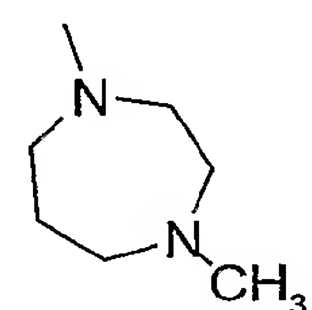
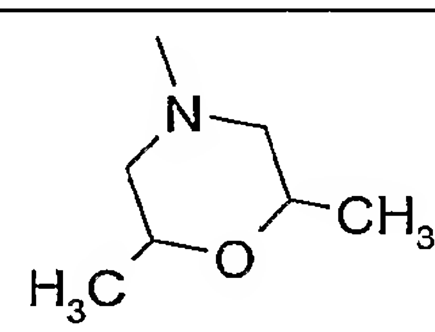
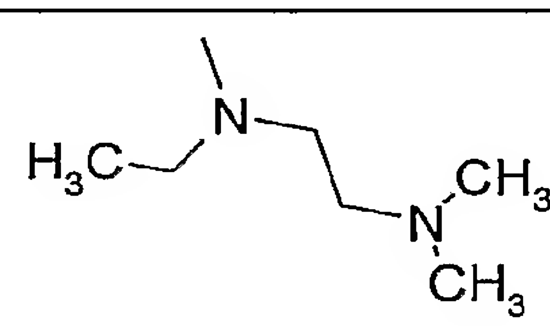
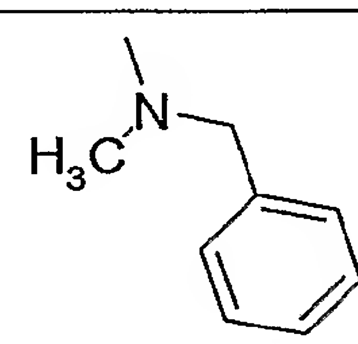
Examples 905 – 941

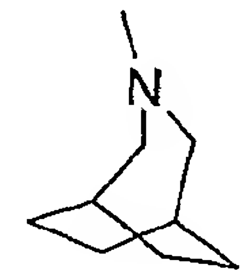
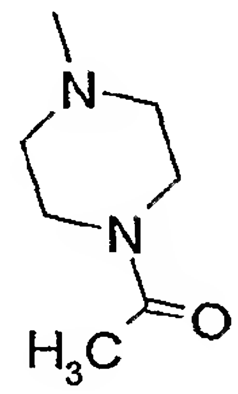
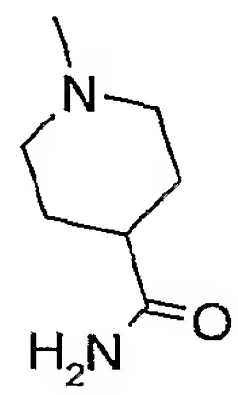
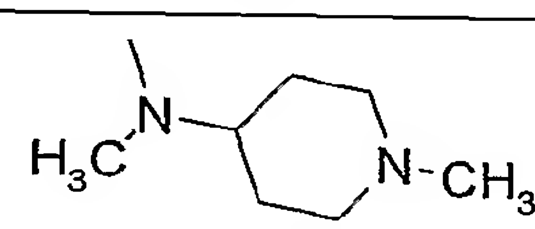
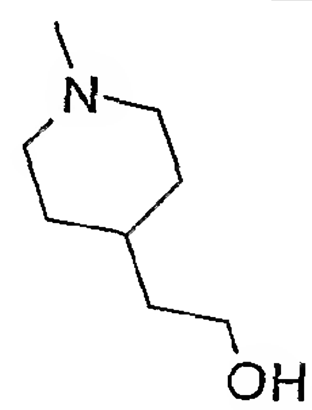
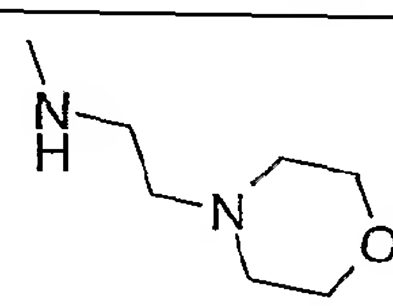
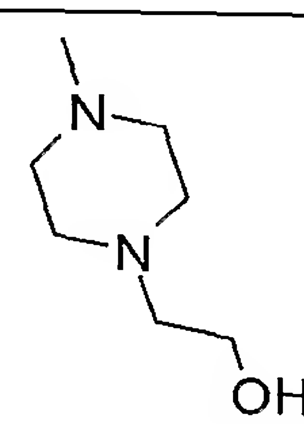
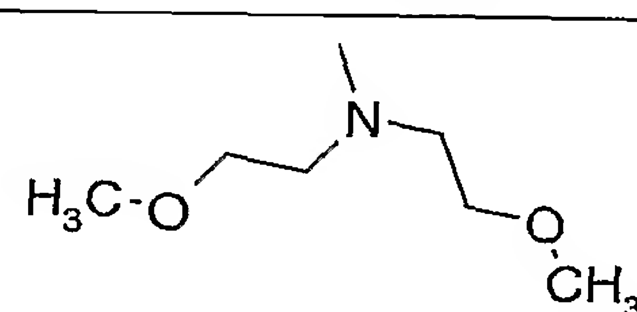
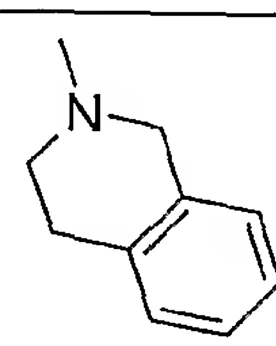
A reagent (0.15 mmol, 1.5 equivalents) from the table below was added to a test tube containing 1-(4-chlorobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine (31 mg, 0.10 mmol, prepared as described in Example 19) and potassium carbonate (approximately 55 mg, 0.40 mmol) in DMF (1 mL). The test tubes were capped and heated at 50 °C for approximately 18 hours and then at 85 °C for 5 hours. The reaction mixtures were filtered and the solvent was removed from the filtrates by vacuum centrifugation. The compounds

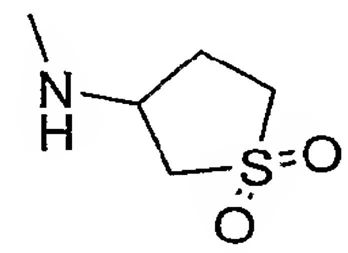
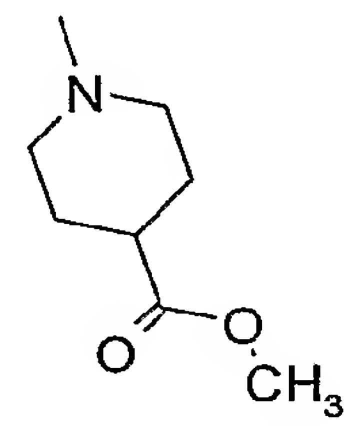
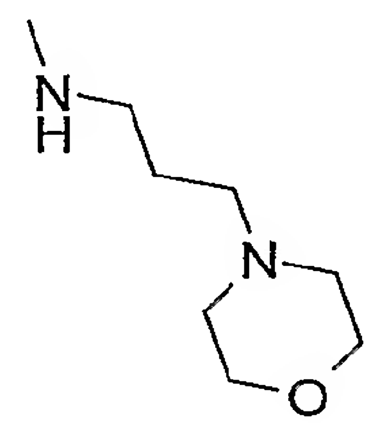
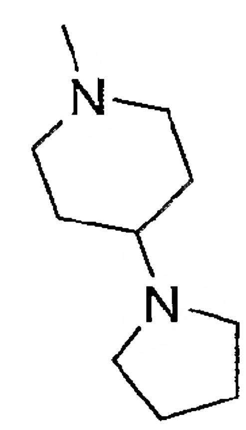
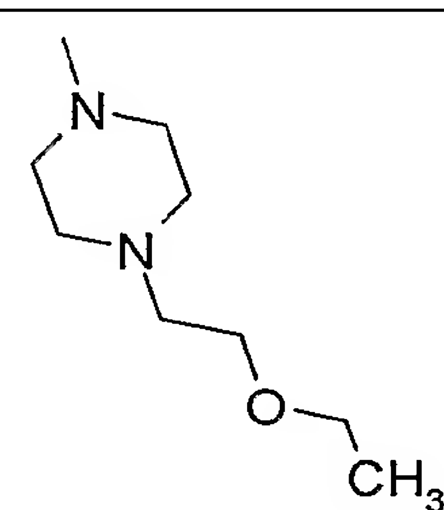
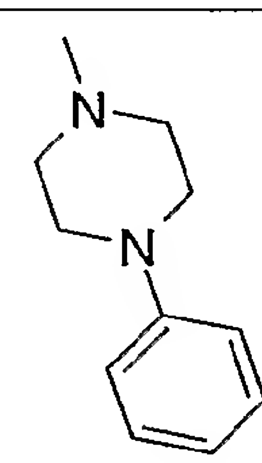
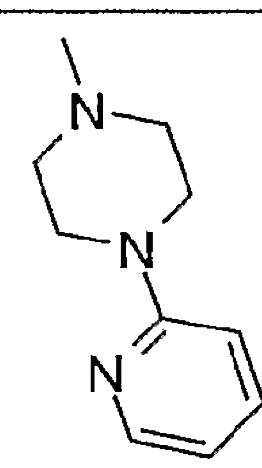
were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

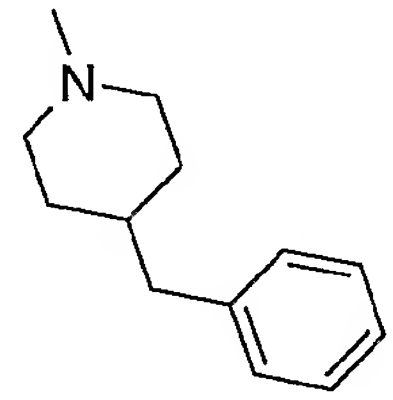
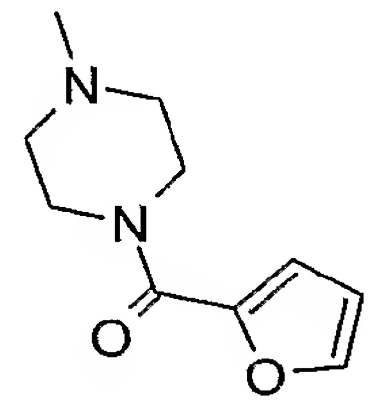


Example	Reagent	R	Measured Mass (M+H)
905	None – starting material		303.1352
906	2-(Methylamino)ethanol		342.2295
907	Cyclopentylamine		352.2509
908	Piperidine		352.2497
909	(R)-3-Hydroxypyrrolidine		354.2297
910	Morpholine		354.2301
911	Thiazolidine		356.1942
912	Cyclohexylamine		366.2661
913	1-Methylpiperazine		367.2617

914	4-Hydroxypiperidine		368.2452
915	Thiomorpholine		370.2053
916	Diethanolamine		372.2402
917	3-Picolylamine		375.2289
918	*N*-Methylfurfurylamine		378.2289
919	*N*-Ethylpiperazine		381.2749
920	*N*-Methylhomopiperazine		381.2764
921	2,6-Dimethylmorpholine		382.2625
922	*N*,*N*-Dimethyl-*N'*-ethylethylenediamine		383.2944
923	*N*-Methylbenzylamine		388.2493

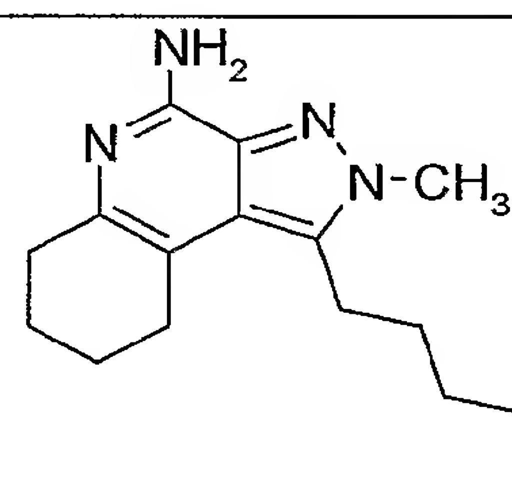
924	3-Azabicyclo[3.2.2]nonane		392.2816
925	1-Acetylpiperazine		395.2555
926	Isonipecotamide		395.2561
927	1-Methyl-4-(methylamino)piperidine		395.2888
928	4-Piperidineethanol		396.2765
929	4-(2-Aminoethyl)morpholine		397.2720
930	*N*-(2-Hydroxyethyl)piperazine		397.2731
931	*bis*(2-Methoxyethyl)amine		400.2716
932	1,2,3,4-Tetrahydroisoquinoline		400.2487

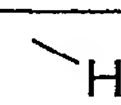
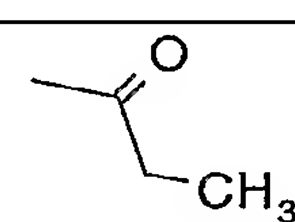
933	1,1-Dioxidotetrahydrothien-3-ylamine		402.1963
934	Methyl isonipecotate		410.2554
935	*N*-(3-Aminopropyl)morpholine		411.2876
936	4-(1-Pyrrolindinyl)-piperidine		421.3071
937	1-(2-Ethoxyethyl)piperazine		425.3028
938	1-Phenylpiperazine		429.2729
939	1-(2-Pyridyl)piperazine		430.2732

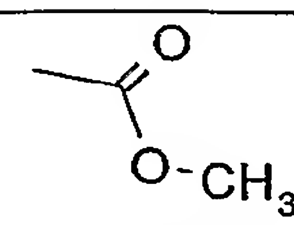
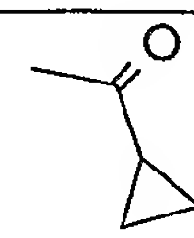
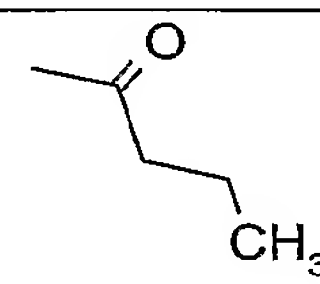
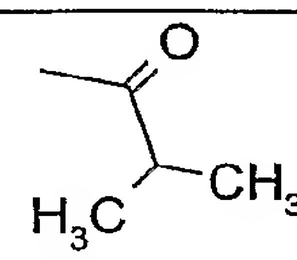
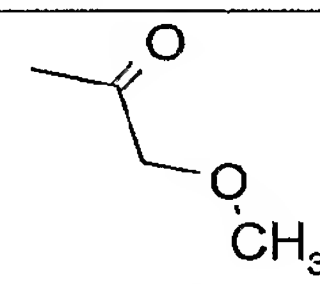
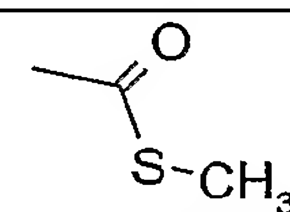
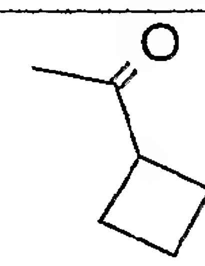
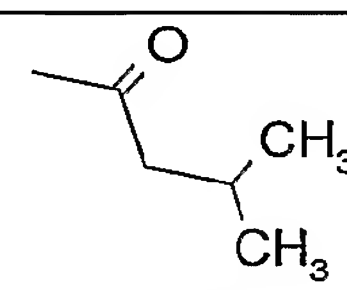
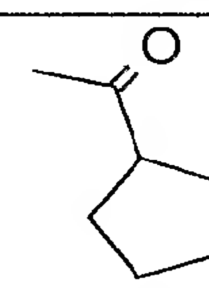
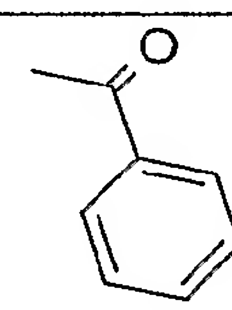
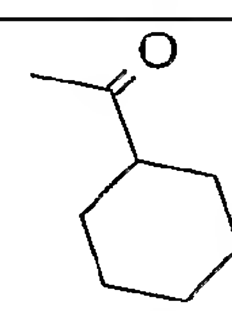
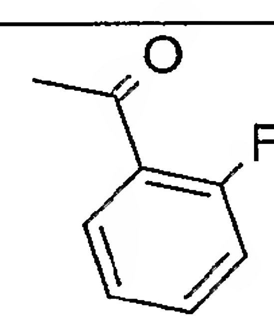
940	4-Benyzylpiperidine		442.2974
941	1-(2-Furoyl)piperazine		447.2495

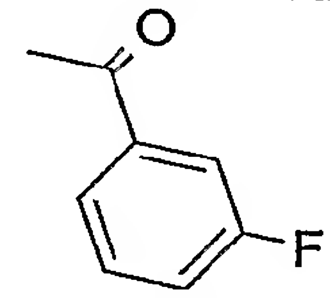
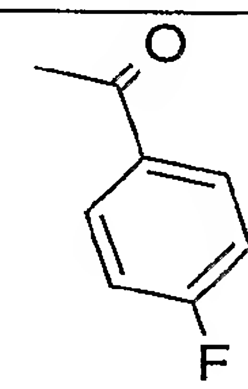
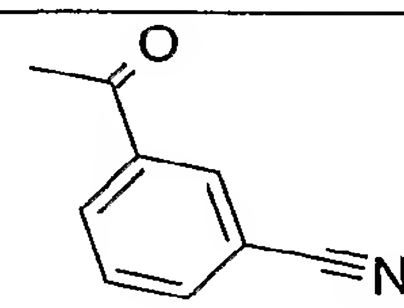
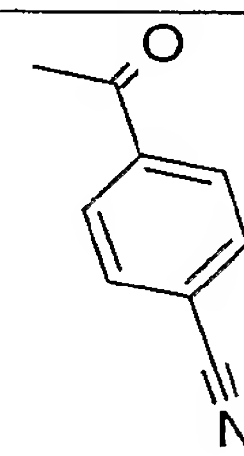
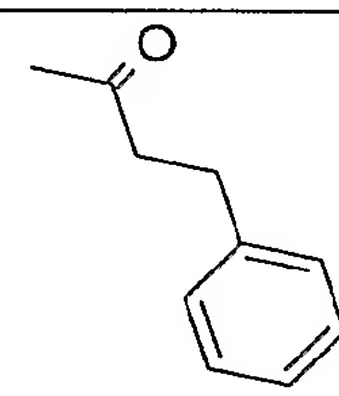
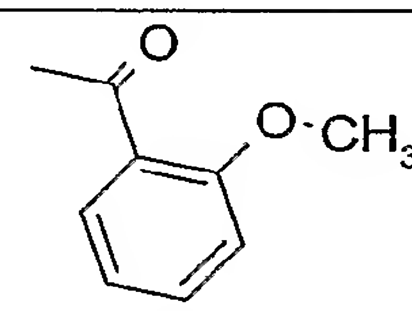
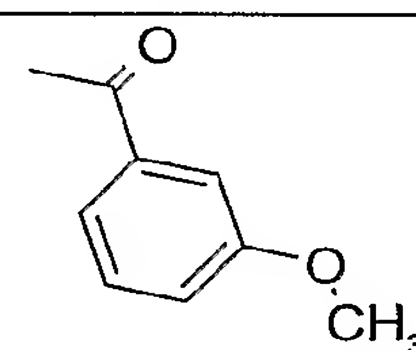
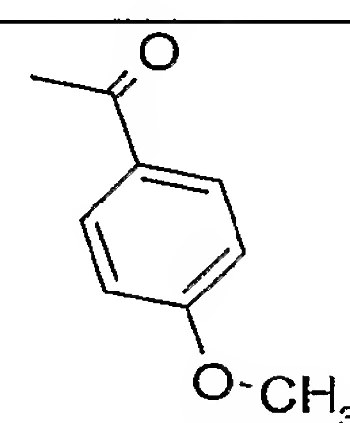
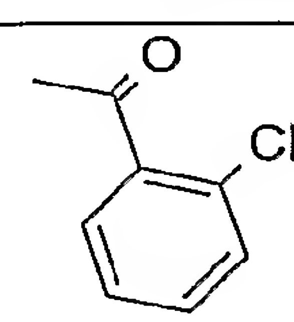
Examples 942 – 1019

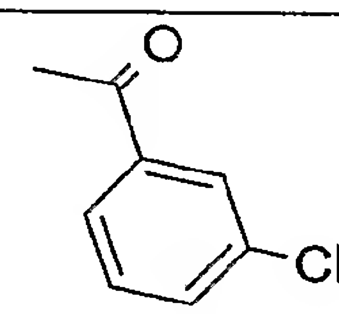
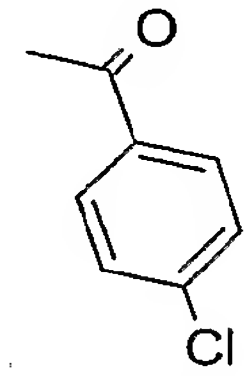
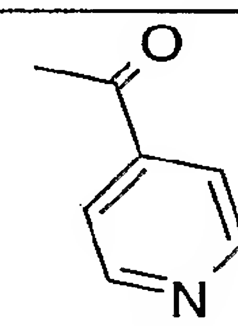
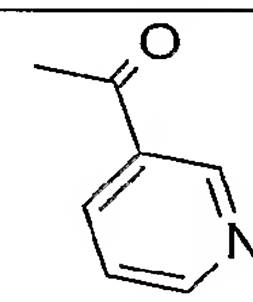
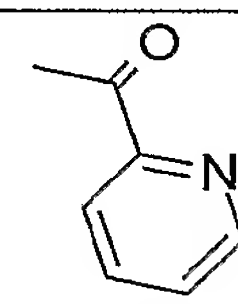
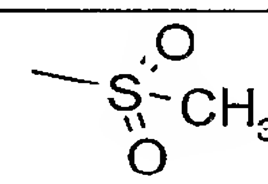
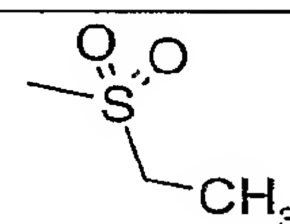
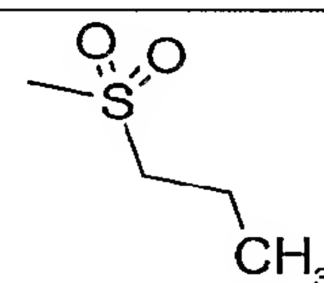
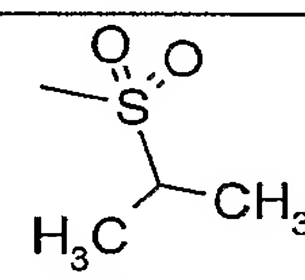
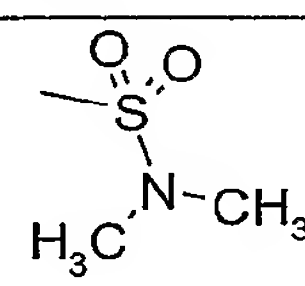
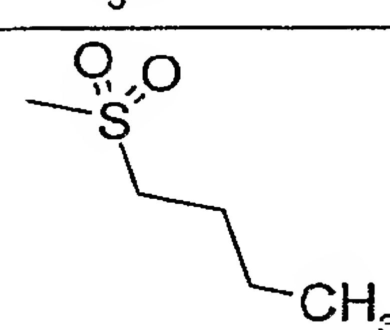
A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(4-aminobutyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (27 mg, 0.10 mmol, prepared as described in Example 589) and *N,N*-diisopropylethylamine (approximately 34 µL, 2 equivalents) in chloroform (1 mL). The test tubes were capped and shaken for about 16 hours. Water (50 µL) was added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

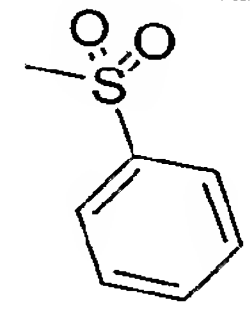
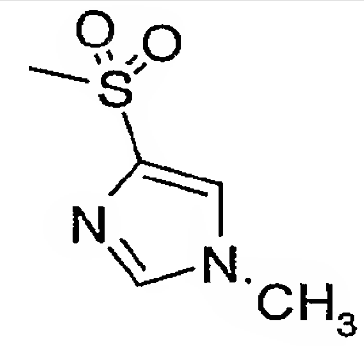
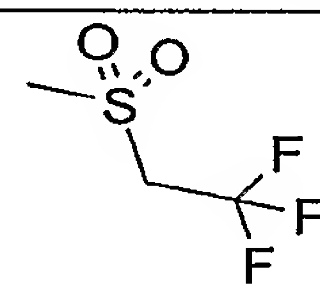
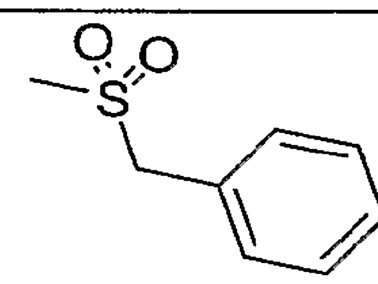
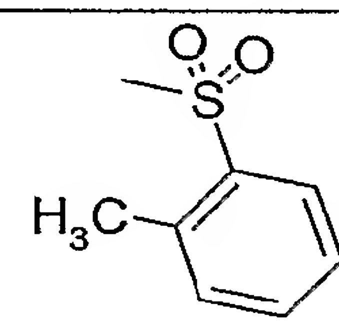
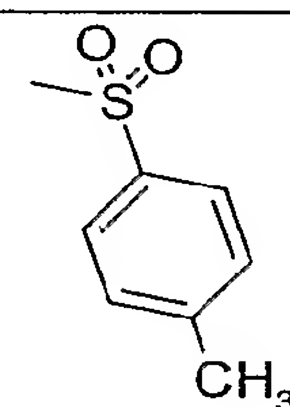
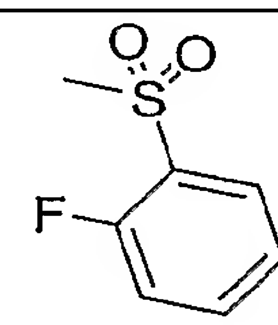
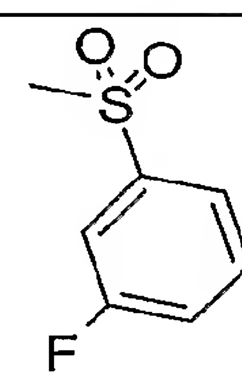
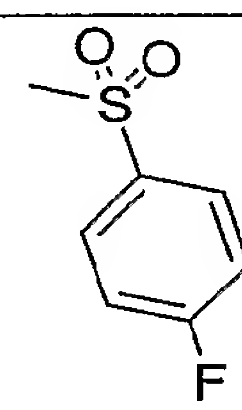


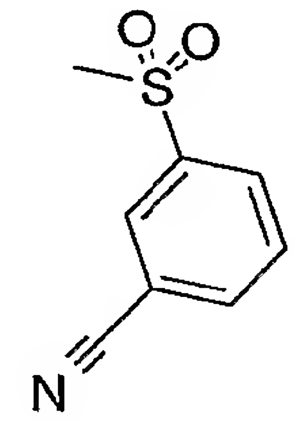
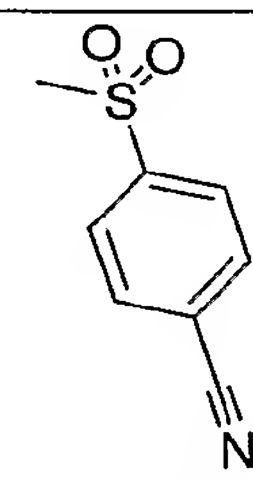
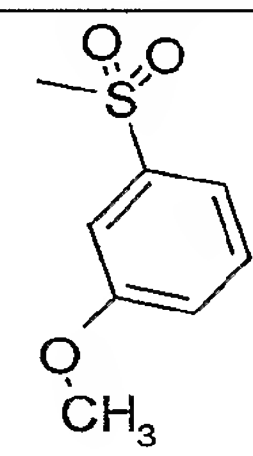
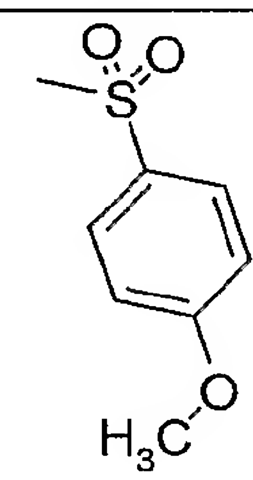
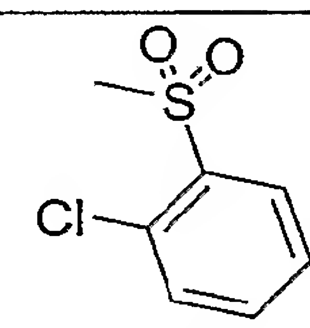
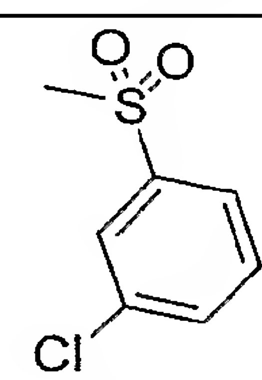
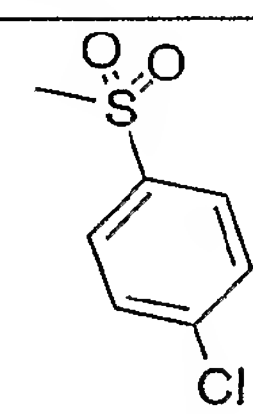
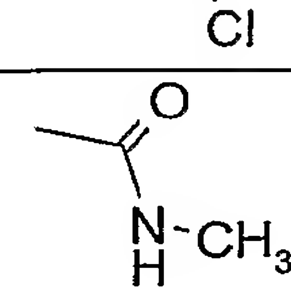
Example	Reagent	R	Measured Mass (M+H)
942	None – starting material		274.2038
943	Propionyl chloride		330.2314

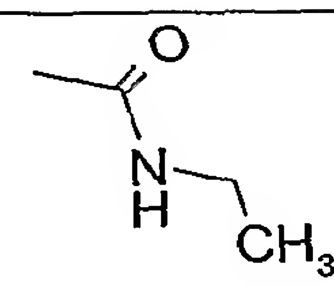
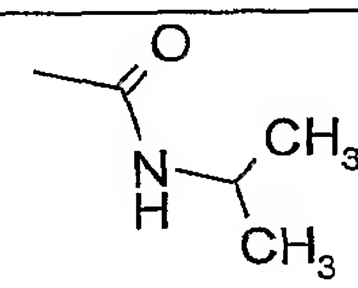
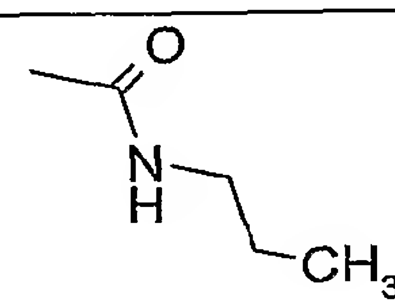
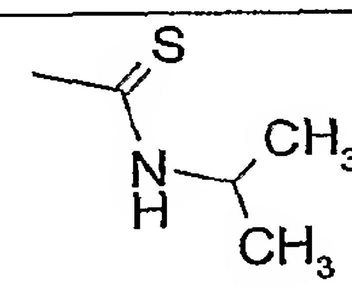
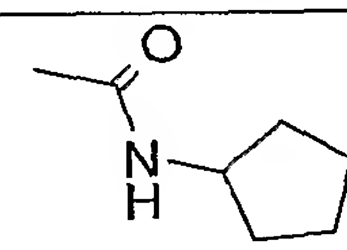
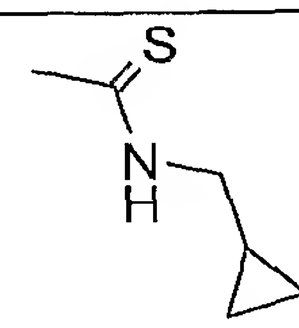
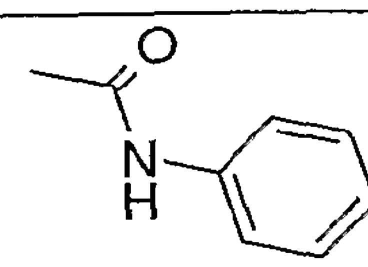
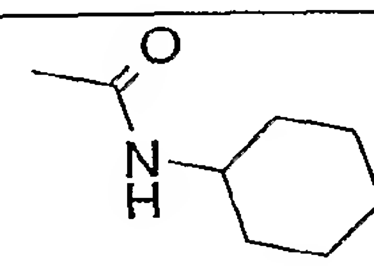
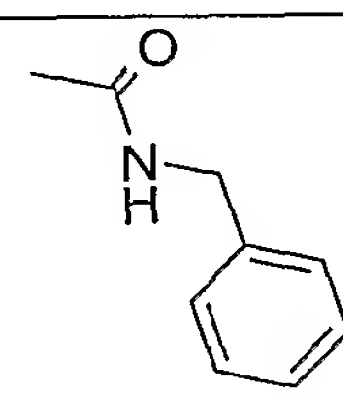
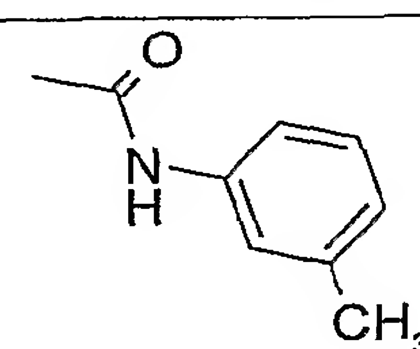
944	Methyl chloroformate		332.2068
945	Cyclopropanecarbonyl chloride		342.2281
946	Butyryl chloride		344.2462
947	Isobutyryl chloride		344.2468
948	Methoxyacetyl chloride		346.2242
949	Methyl chlorothiolformate		348.1872
950	Cyclobutanecarbonyl chloride		356.2471
951	Isovaleryl chloride		358.2617
952	Cyclopentanecarbonyl chloride		370.2637
953	Benzoyl chloride		378.2315
954	Cyclohexanecarbonyl chloride		384.2777
955	2-Fluorobenzoyl chloride		396.2228

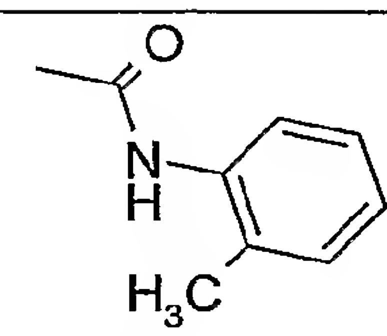
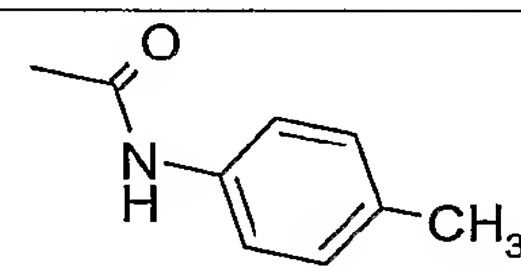
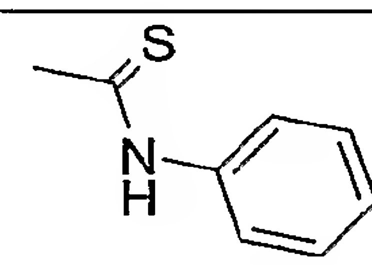
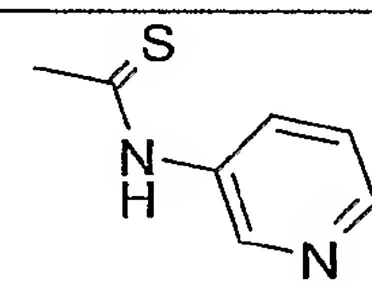
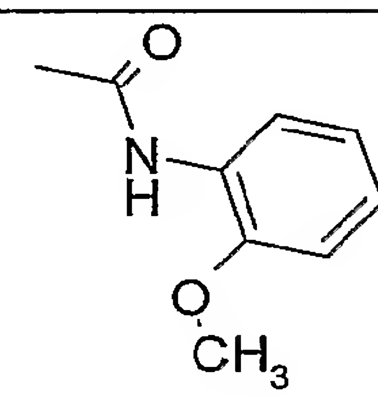
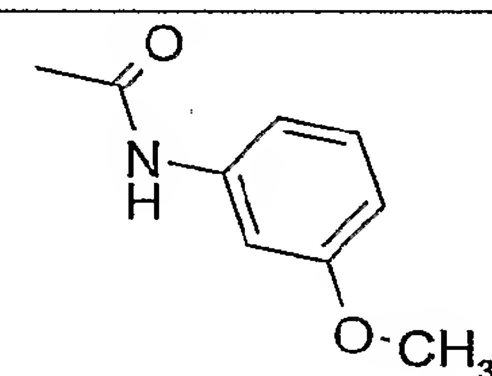
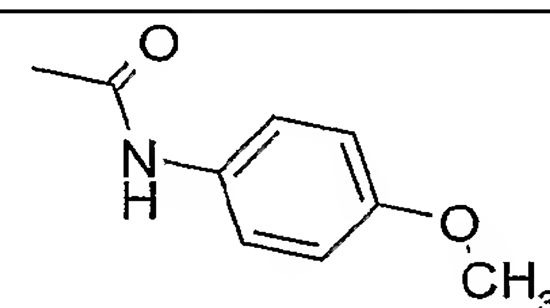
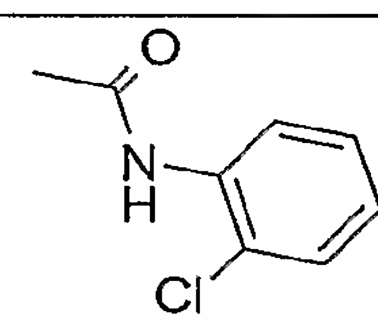
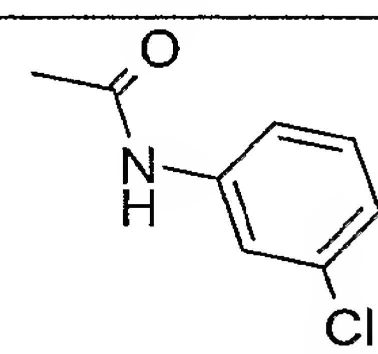
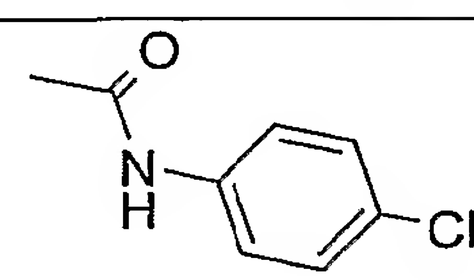
956	3-Fluorobenzoyl chloride		396.2219
957	4-Fluorobenzoyl chloride		396.2228
958	3-Cyanobenzoyl chloride		403.2255
959	4-Cyanobenzoyl chloride		403.2274
960	Hydrocinnamoyl chloride		406.2613
961	2-Methoxybenzoyl chloride		408.2415
962	3-Methoxybenzoyl chloride		408.2403
963	*p*-Anisoyl chloride		408.2409
964	2-Chlorobenzoyl chloride		412.1929

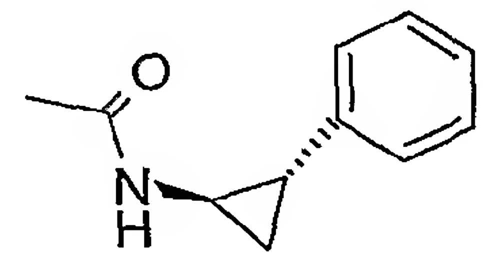
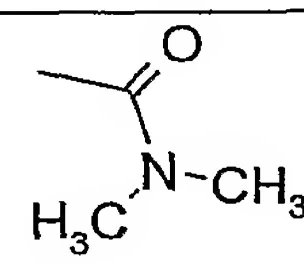
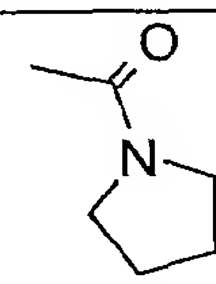
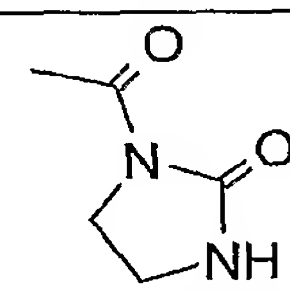
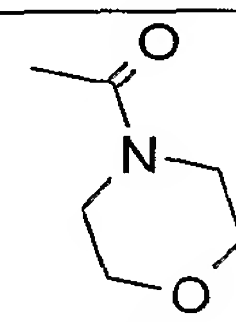
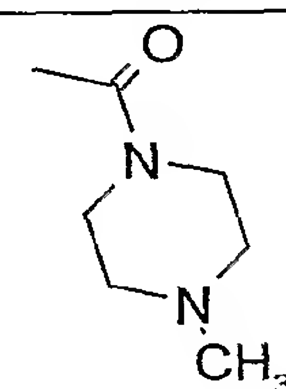
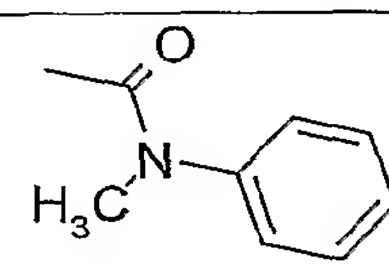
965	3-Chlorobenzoyl chloride		412.1936
966	4-Chlorobenzoyl chloride		412.1929
967	Isonicotinoyl chloride hydrochloride		379.2263
968	Nicotinoyl chloride hydrochloride		379.2217
969	Picolinoyl chloride hydrochloride		379.2234
970	Methanesulfonyl chloride		352.1825
971	Ethanesulfonyl chloride		366.1987
972	1-Propanesulfonyl chloride		380.2142
973	Isopropylsulfonyl chloride		380.2150
974	Dimethylsulfamoyl chloride		381.2038
975	1-Butanesulfonyl chloride		394.2293

976	Benzenesulfonyl chloride		414.1946
977	1-Methylimidazole-4-sulfonyl chloride		418.2022
978	2,2,2-Trifluoroethanesulfonyl chloride		420.1650
979	*alpha*-Toluenesulfonyl chloride		428.2090
980	*o*-Toluenesulfonyl chloride		428.2122
981	*p*-Toluenesulfonyl chloride		428.2105
982	2-Fluorobenzenesulfonyl chloride		432.1891
983	3-Fluorobenzenesulfonyl chloride		432.1877
984	4-Fluorobenzenesulfonyl chloride		432.1838

985	3-Cyanobenzenesulfonyl chloride		439.1921
986	4-Cyanobenzenesulfonyl chloride		439.1921
987	3-Methoxybenzenesulfonyl chloride		444.2036
988	4-Methoxybenzenesulfonyl chloride		444.2082
989	2-Chlorobenzenesulfonyl chloride		448.1583
990	3-Chlorobenzenesulfonyl chloride		448.1584
991	4-Chlorobenzenesulfonyl chloride		448.1583
992	Methyl isocyanate		331.2276

993	Ethyl isocyanate		345.2416
994	Isopropyl isocyanate		359.2588
995	*N*-Propyl isocyanate		359.2568
996	Isopropyl isothiocyanate		375.2342
997	Cyclopentyl isocyanate		385.2722
998	Cyclopropylmethyl isothiocyanate		387.2356
999	Phenyl isocyanate		393.2427
1000	Cyclohexyl isocyanate		399.2901
1001	Benzyl isocyanate		407.2578
1002	*m*-Tolyl isocyanate		407.2584

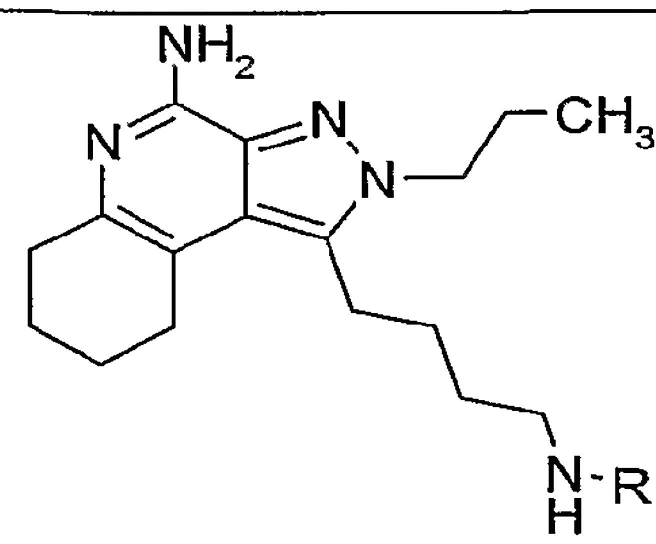
1003	*o*-Tolyl isocyanate		407.2581
1004	*p*-Tolyl isocyanate		407.2563
1005	Phenyl isothiocyanate		409.2182
1006	3-Pyridyl isothiocyanate		410.2164
1007	2-Methoxyphenyl isocyanate		423.2523
1008	3-Methoxyphenyl isocyanate		423.2486
1009	4-Methoxyphenyl isocyanate		423.2512
1010	2-Chlorophenyl isocyanate		427.2027
1011	3-Chlorophenyl isocyanate		427.2027
1012	4-Chlorophenyl isocyanate		427.2030

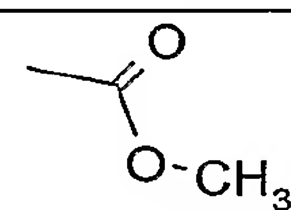
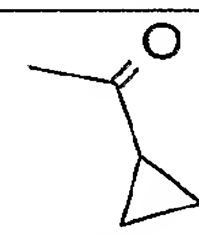
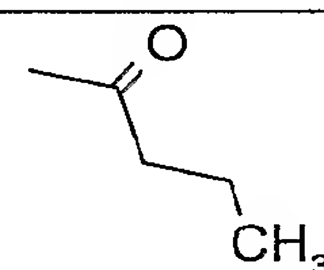
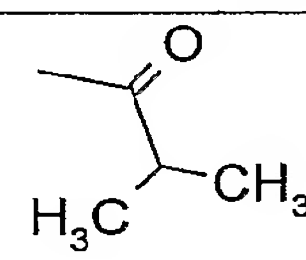
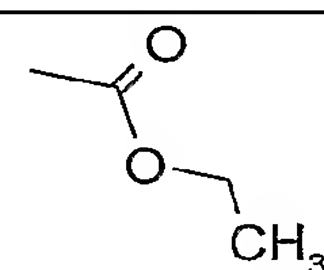
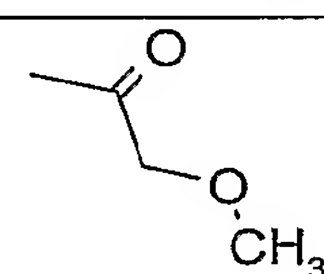
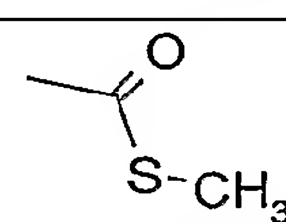
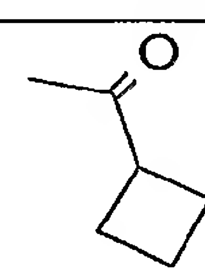
1013	*trans*-2-Phenylcyclopropyl isocyanate		433.2676
1014	*N,N*-Dimethylcarbamoyl chloride		345.2416
1015	1-Pyrrolidinecarbonyl chloride		371.2584
1016	2-Oxo-1-imidazolidinecarbonyl chloride		386.2310
1017	4-Morpholinylcarbonyl chloride		387.2515
1018	4- Methyl-1-Piperazinecarbonyl chloride		400.2810
1019	*N*-Methyl-*N*-Phenylcarbamoyl chloride		407.2577

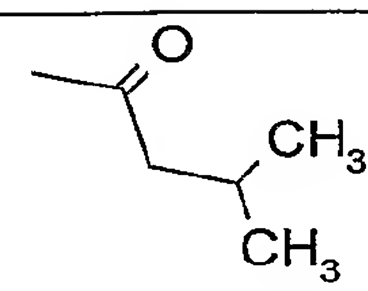
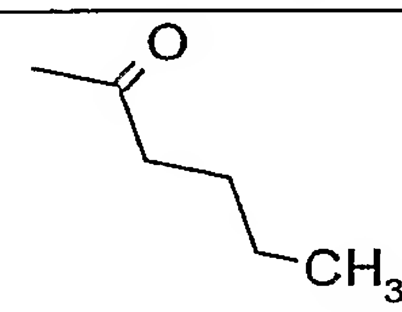
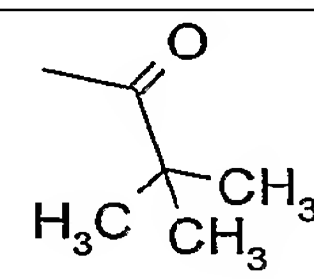
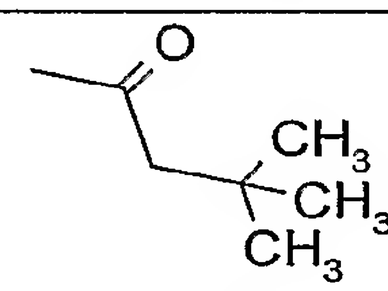
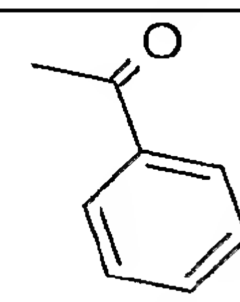
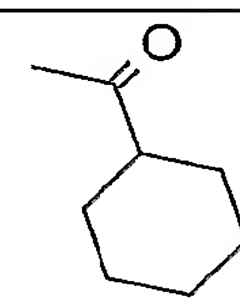
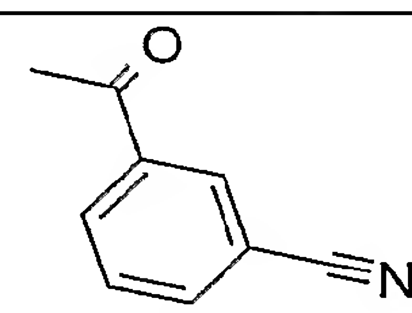
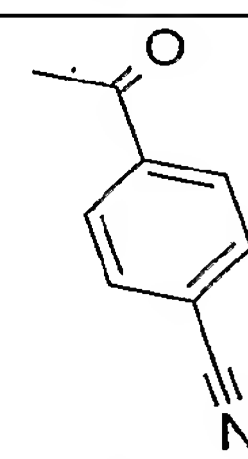
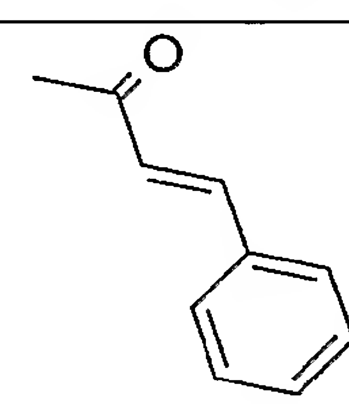
Examples 1020 – 1097

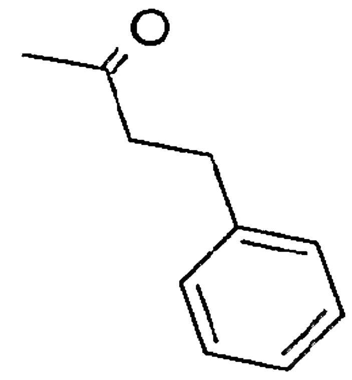
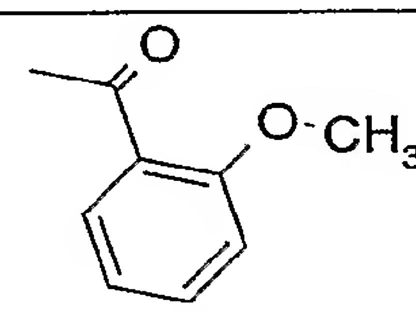
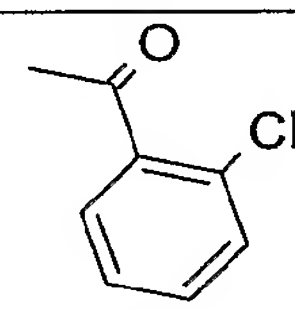
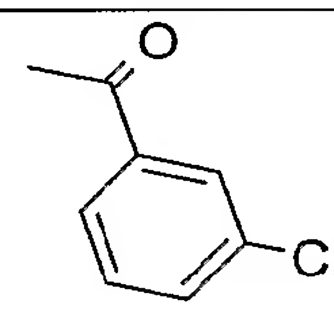
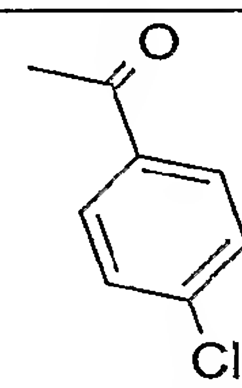
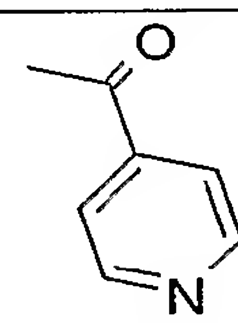
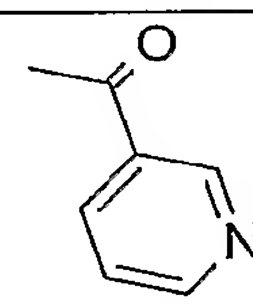
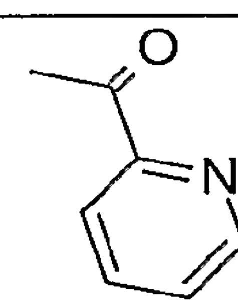
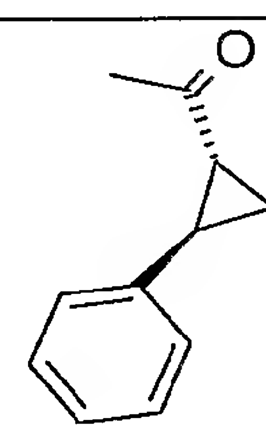
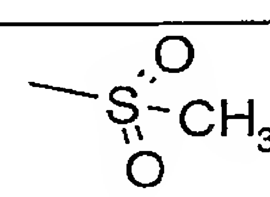
A reagent (0.12 mmol, 1.2 equivalents) from the table below was added to a test tube containing 1-(4-aminobutyl)-2-propyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine *tris*-trifluoroacetate (64 mg, 0.10 mmol, prepared as described in Example 578) and *N,N*-diisopropylethylamine (approximately 90 µL, 5 equivalents) in *N,N*-dimethylacetamide (1 mL). The test tubes were capped and shaken for about 16 hours. Water (30 µL) was added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table

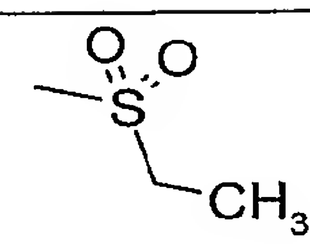
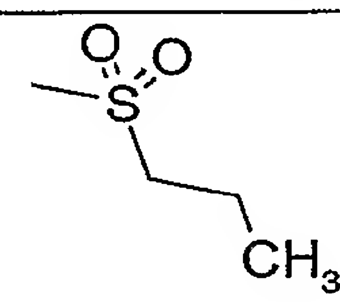
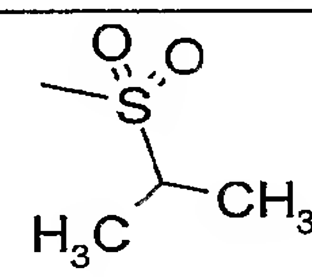
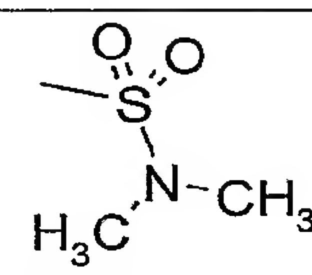
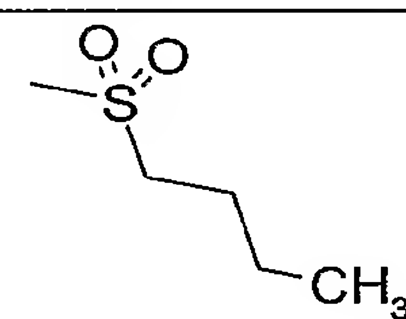
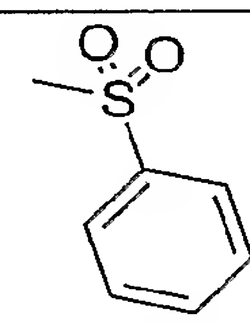
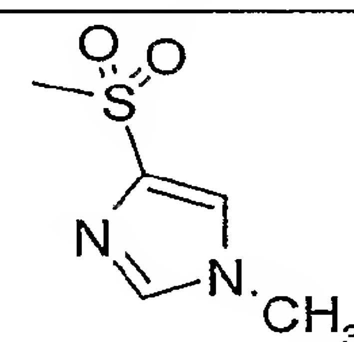
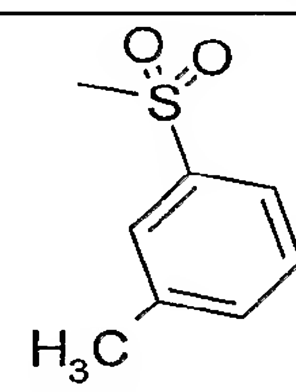
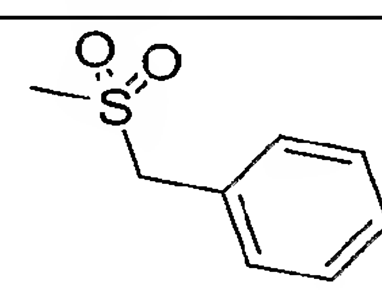
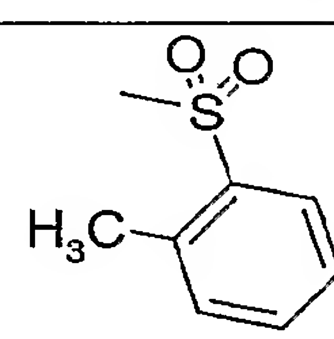
below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

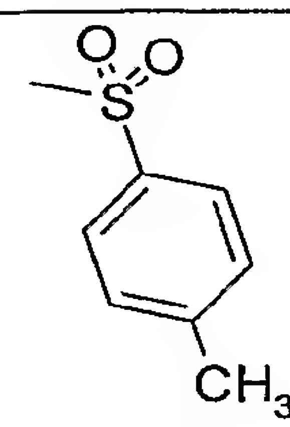
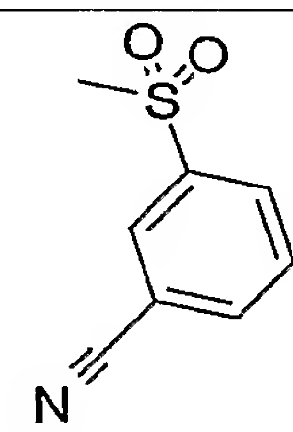
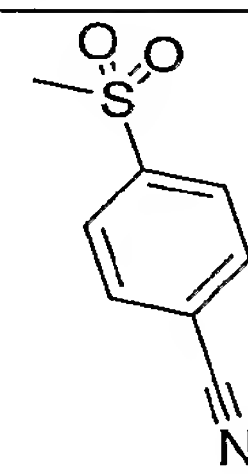
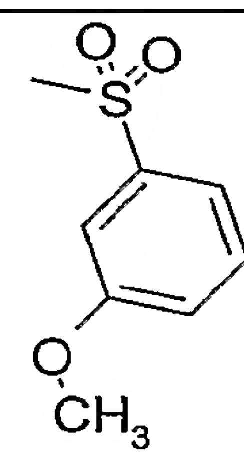
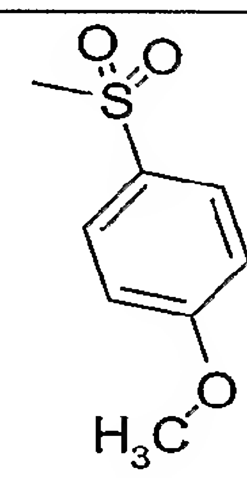
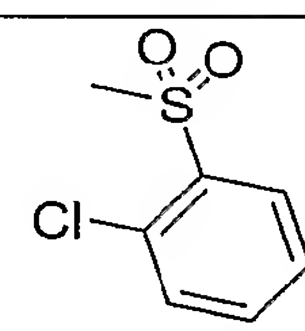
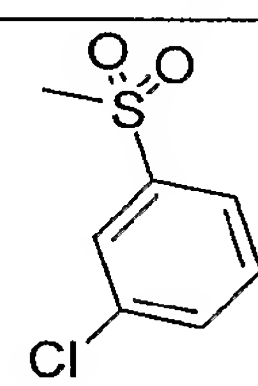


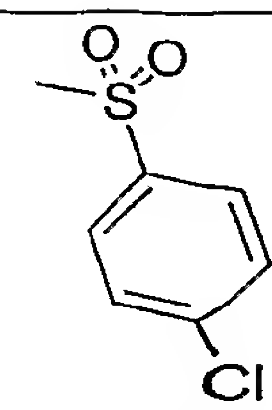
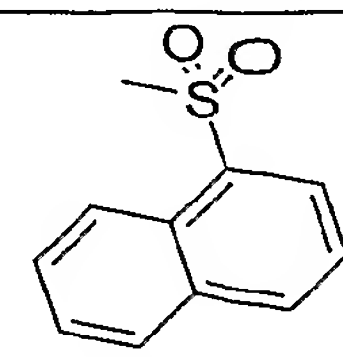
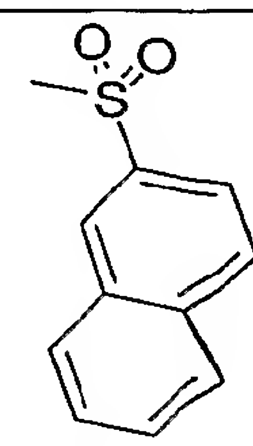
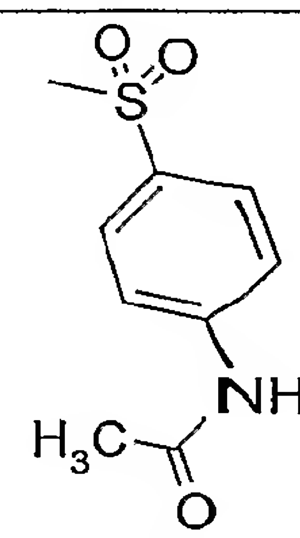
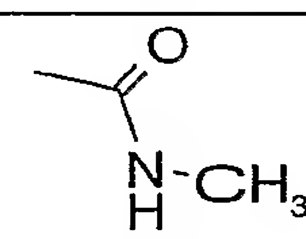
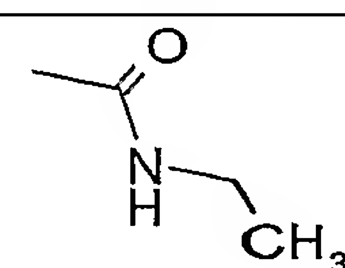
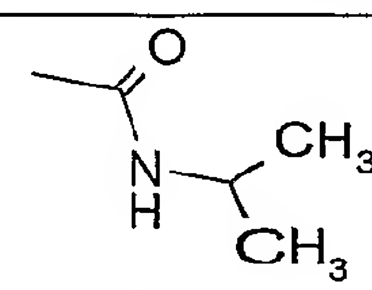
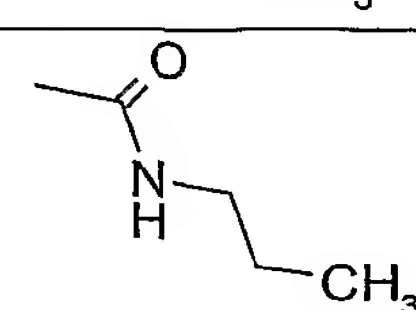
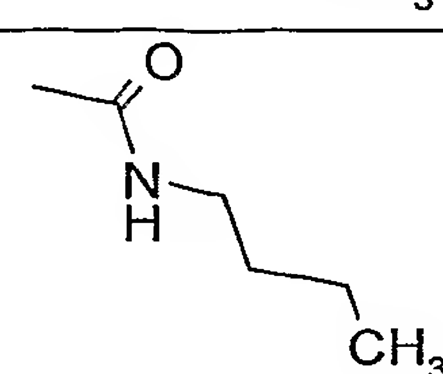
Example	Reagent	R	Measured Mass (M+H)
1020	None – starting material		302.2356
1021	Methyl chloroformate		360.2431
1022	Cyclopropanecarbonyl chloride		370.2581
1023	Butryrl chloride		372.2793
1024	Isobutyryl chloride		372.2797
1025	Ethyl chloroformate		374.2581
1026	Methoxyacetyl chloride		374.2524
1027	Methyl chlorothiolformate		376.2200
1028	Cyclobutanecarbonyl chloride		384.2800

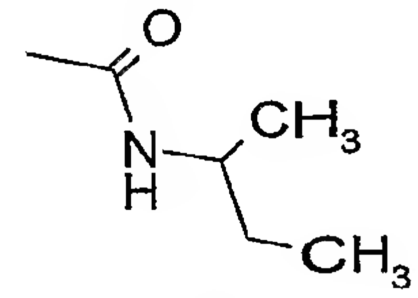
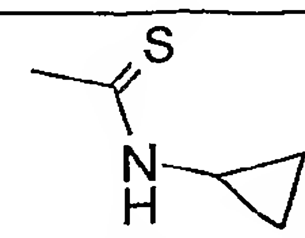
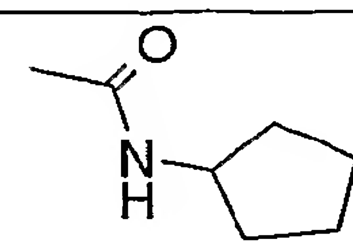
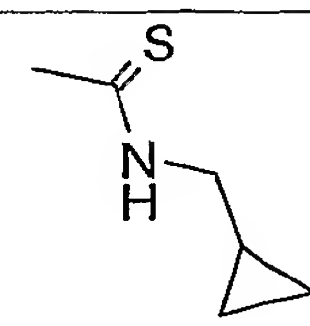
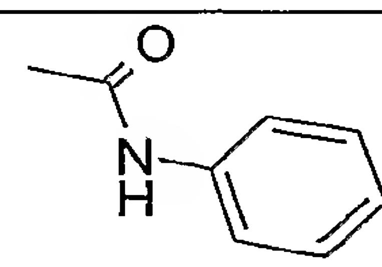
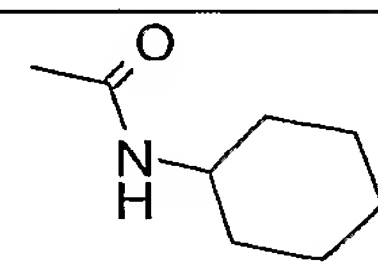
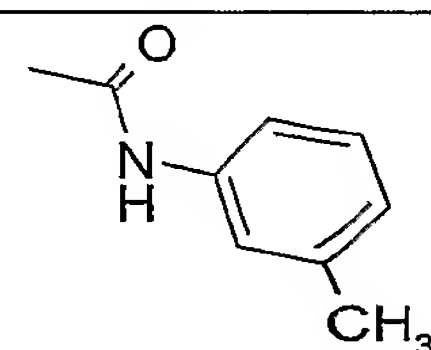
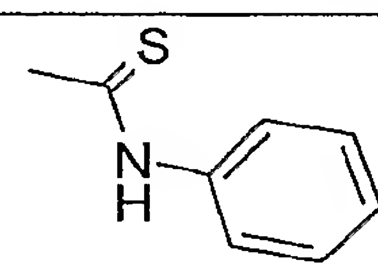
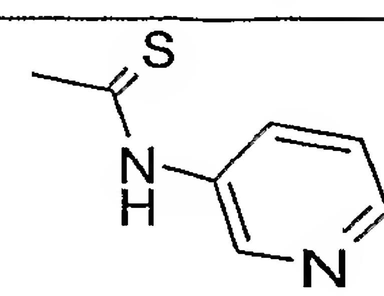
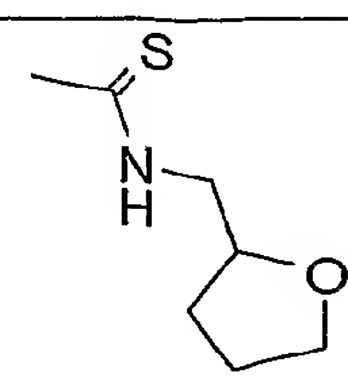
1029	Isovaleryl chloride		386.2942
1030	Pentanoyl chloride		386.2930
1031	Pivaloyl chloride		386.2955
1032	*tert*-Butylacetyl chloride		400.3100
1033	Benzoyl chloride		406.2637
1034	Cyclohexanecarbonyl chloride		412.3082
1035	3-Cyanobenzoyl chloride		431.2566
1036	4-Cyanobenzoyl chloride		431.2582
1037	Cinnamoyl chloride		432.2789

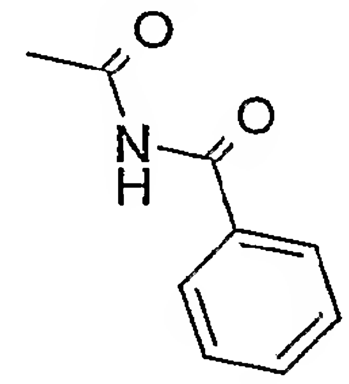
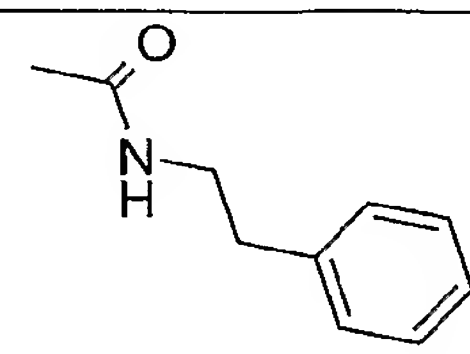
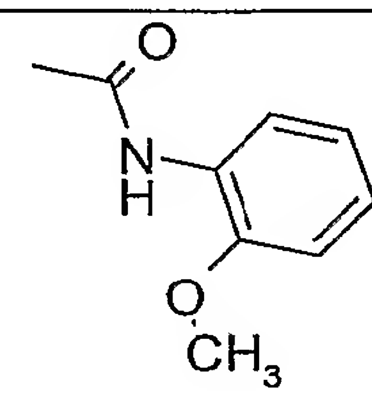
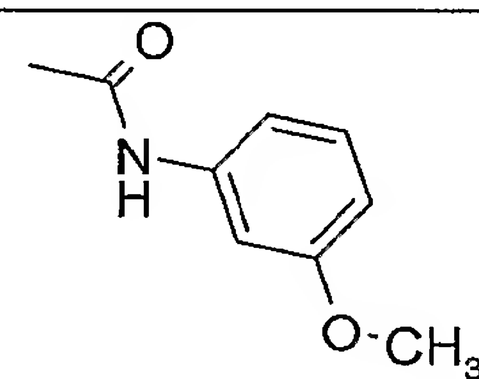
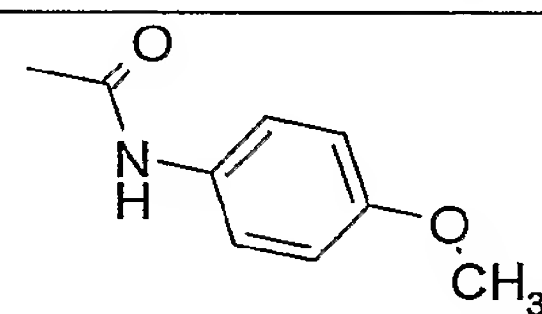
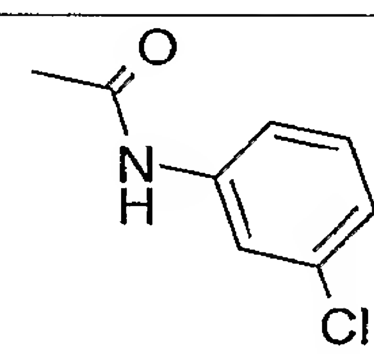
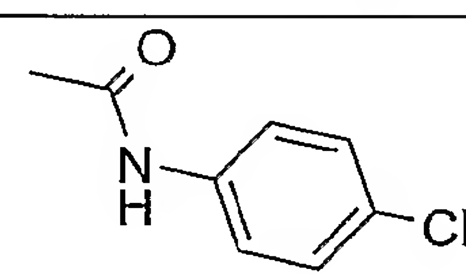
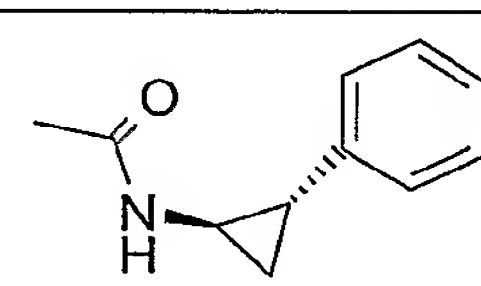
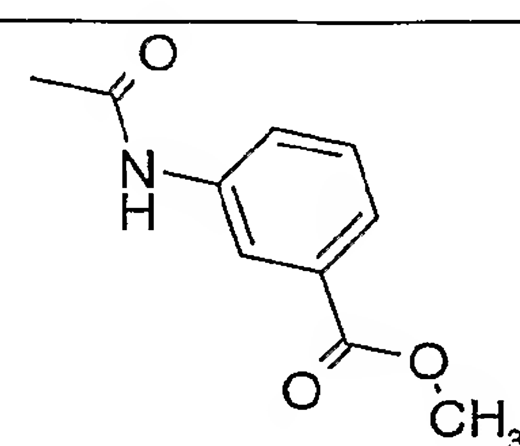
1038	Hydrocinnamoyl chloride		434.2884
1039	2-Methoxylbenzoyl chloride		436.2724
1040	2-Chlorobenzoyl chloride		440.2225
1041	3-Chlorobenzoyl chloride		440.2231
1042	4-Chlorobenzoyl chloride		440.2261
1043	Isonicotinoyl chloride hydrochloride		407.2575
1044	Nicotinoyl chloride hydrochloride		407.2576
1045	Picolinoyl chloride hydrochloride		407.2582
1046	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		446.2876
1047	Methanesulfonyl chloride		380.2112

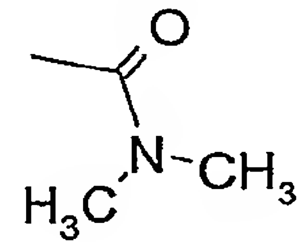
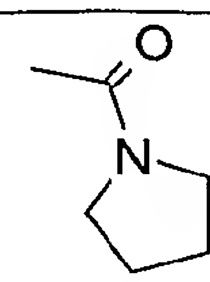
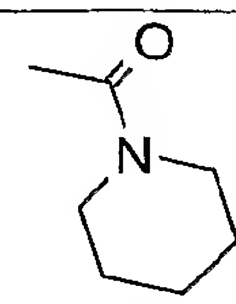
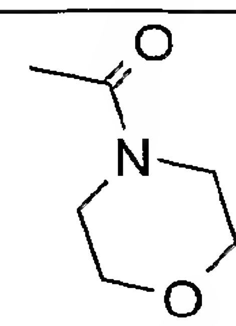
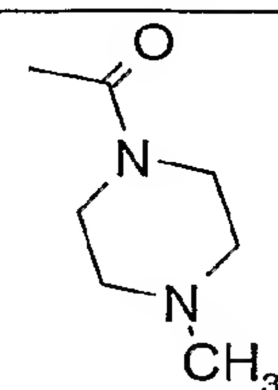
1048	Ethanesulfonyl chloride		394.2269
1049	1-Propanesulfonyl chloride		408.2450
1050	Isopropylsulfonyl chloride		408.2448
1051	Dimethylsulfamoyl chloride		409.2384
1052	1-Butanesulfonyl chloride		422.2617
1053	Benzenesulfonyl chloride		442.2272
1054	1-Methylimidazole-4-sulfonyl chloride		446.2353
1055	3-Methylbenzenesulfonyl chloride		456.2474
1056	*alpha*-Toluenesulfonyl chloride		456.2435
1057	*o*-Toluenesulfonyl chloride		456.2475

1058	*p*-Toluenesulfonyl chloride		456.2390
1059	3-Cyanobenzenesulfonyl chloride		467.2200
1060	4-Cyanobenzenesulfonyl chloride		467.2187
1061	3-Methoxybenzenesulfonyl chloride		472.2384
1062	4-Methoxybenzenesulfonyl chloride		472.2398
1063	2-Chlorobenzenesulfonyl chloride		476.1908
1064	3-Chlorobenzenesulfonyl chloride		476.1861

1065	4-Chlorobenzenesulfonyl chloride		476.1846
1066	1-Naphthalenesulfonyl chloride		492.2451
1067	2-Naphthalenesulfonyl chloride		492.2414
1068	*N*-Acetylsulfanilyl chloride		499.2519
1069	Methyl isocyanate		359.2596
1070	Ethyl isocyanate		373.2702
1071	Isopropyl isocyanate		387.2855
1072	*N*-Propyl isocyanate		387.2852
1073	*N*-Butyl isocyanate		401.3009

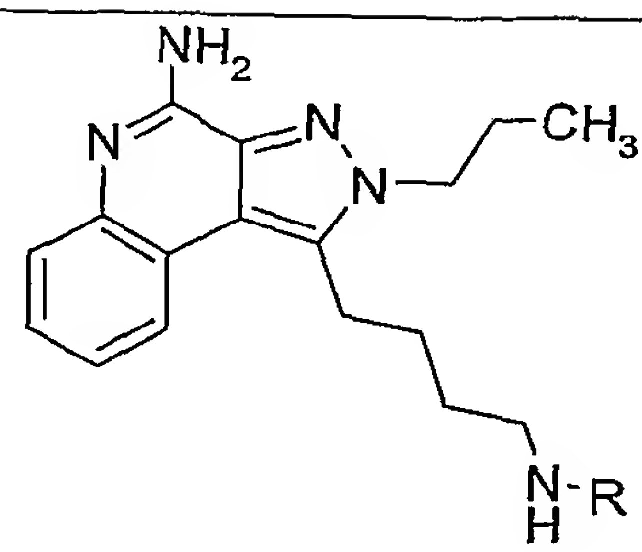
1074	*sec*-Butyl isocyanate		401.3026
1075	Cyclopropyl isothiocyanate		401.2458
1076	Cyclopentyl isocyanate		413.2993
1077	Cyclopropylmethyl isothiocyanate		415.2605
1078	Phenyl isocyanate		421.2702
1079	Cyclohexyl isocyanate		427.3229
1080	*m*-Tolyl isocyanate		435.2876
1081	Phenyl isothiocyanate		437.2459
1082	3-Pyridyl isothiocyanate		438.2480
1083	2-Tetrahydrofurfuryl isothiocyanate		445.2741

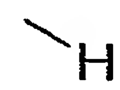
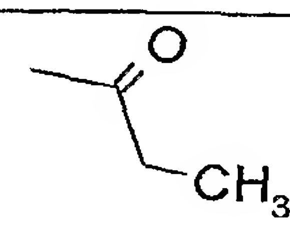
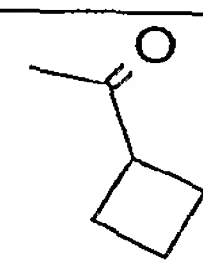
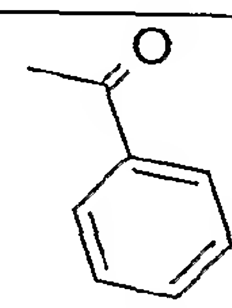
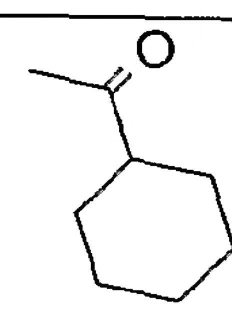
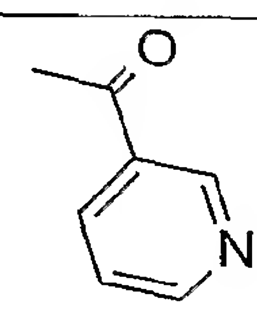
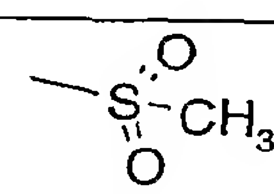
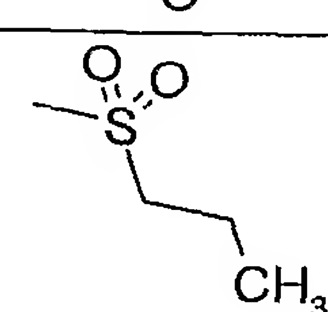
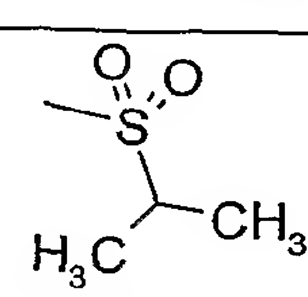
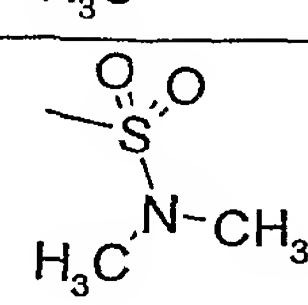
1084	Benzoyl isocyanate		449.2674
1085	2-Phenylethyl isocyanate		449.3064
1086	2-Methoxylphenyl isocyanate		451.2864
1087	3-Methoxylphenyl isocyanate		451.2798
1088	4-Methoxylphenyl isocyanate		451.2860
1089	3-Chlorophenyl isocyanate		455.2350
1090	4-Chlorophenyl isocyanate		455.2345
1091	*trans*-2-Phenylcyclopropyl isocyanate		461.3076
1092	3-Carbomethoxyphenyl isocyanate		479.2800

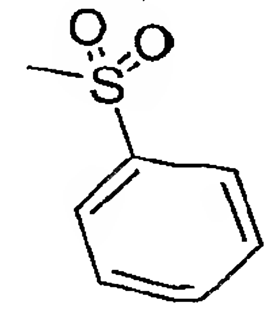
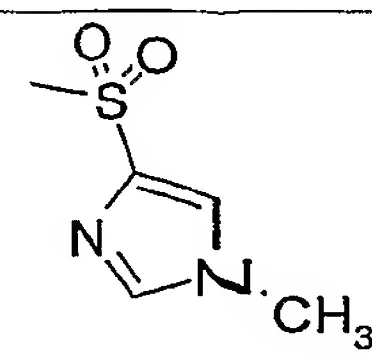
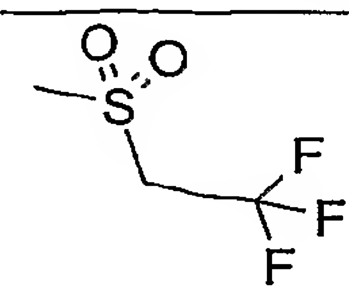
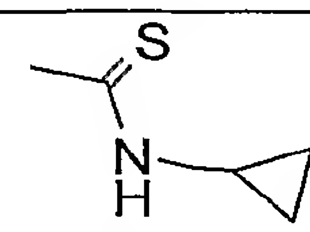
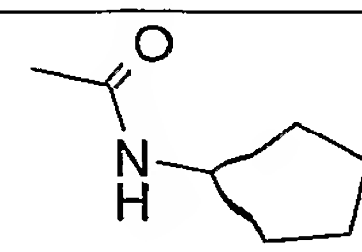
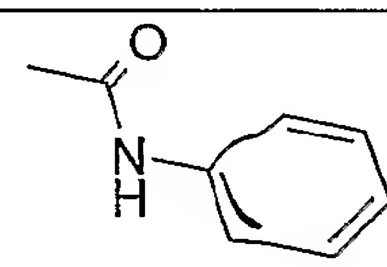
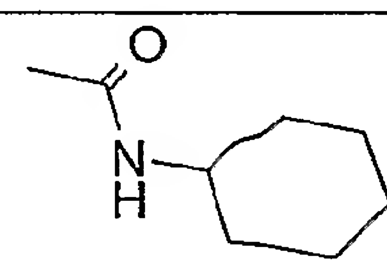
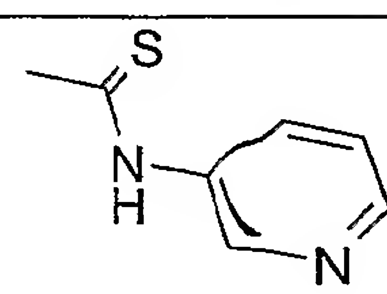
1093	*N,N*-Dimethylcarbamoyl chloride		373.2736
1094	1-Pyrrolidinecarbonyl chloride		399.2891
1095	1-Piperidinecarbonyl chloride		413.2986
1096	4-Morpholinecarbonyl chloride		415.2802
1097	4-Methyl-1-Piperazinecarbonyl chloride		428.3176

Examples 1098 – 1115

A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(4-aminobutyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (30 mg, 0.10 mmol, prepared as described in Example 577) and *N,N*-diisopropylethylamine (approximately 36 µL, 2 equivalents) in chloroform (1 mL). The test tubes were capped and shaken for about 4 hours. Two drops of water were added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



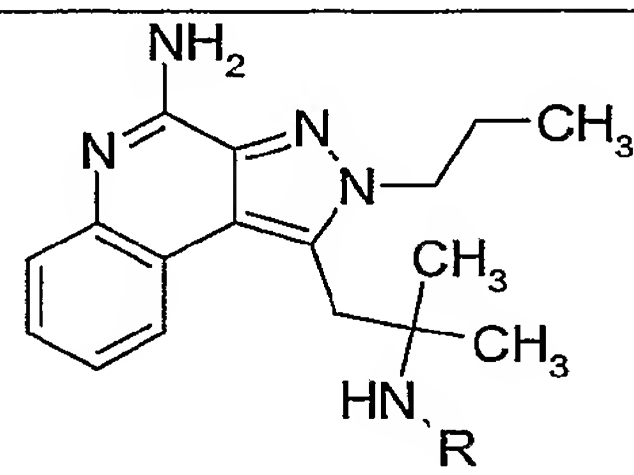
Example	Reagent	R	Measured Mass (M+H)
1098	None – starting material		298.2036
1099	Propionyl chloride		354.2326
1100	Cyclobutanecarbonyl chloride		380.2464
1101	Benzoyl chloride		402.2332
1102	Cyclohexanecarbonyl chloride		408.2801
1103	Nicotinoyl chloride hydrochloride		403.2280
1104	Methanesulfonyl chloride		376.1839
1105	1-Propanesulfonyl chloride		404.2154
1106	Isopropylsulfonyl chloride		404.2087
1107	Dimethylsulfamoyl chloride		405.2098

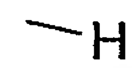
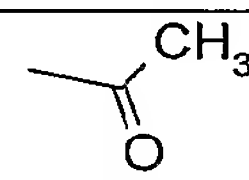
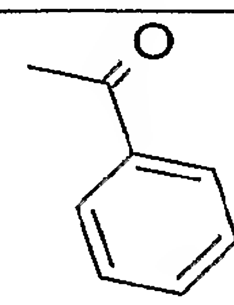
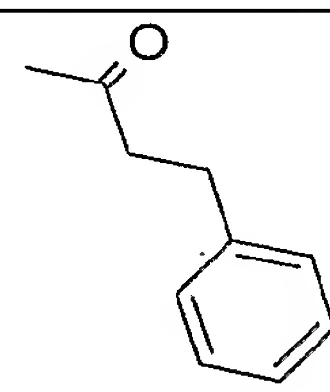
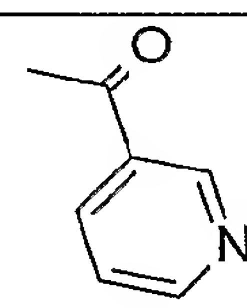
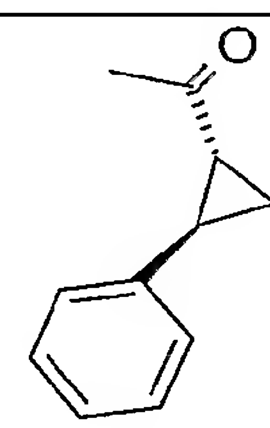
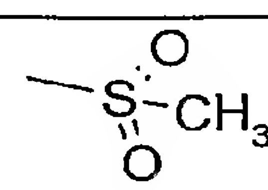
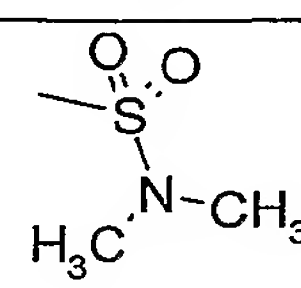
1108	Benzenesulfonyl chloride		438.1996
1109	1-Methylimidazole-4-sulfonyl chloride		442.2025
1110	2,2,2-Trifluoroethanesulfonyl chloride		444.1700
1111	Cyclopropyl isothiocyanate		397.2207
1112	Cyclopentyl isocyanate		409.2737
1113	Phenyl isocyanate		417.2438
1114	Cyclohexyl isocyanate		423.2903
1115	3-Pyridyl isothiocyanate		434.2153

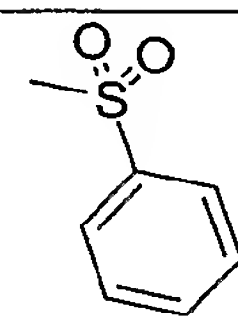
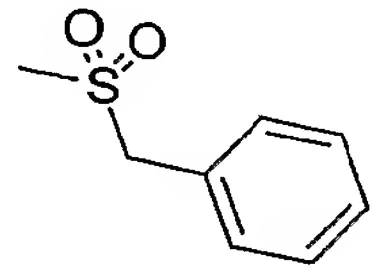
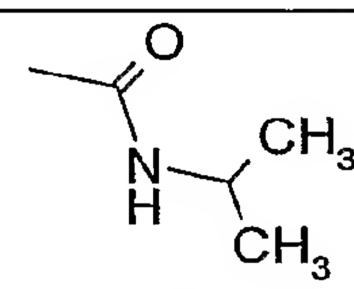
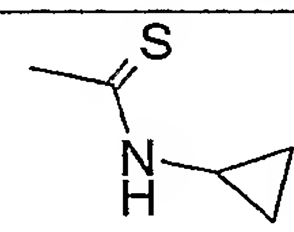
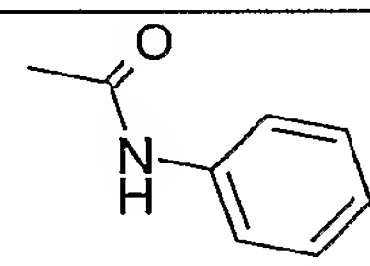
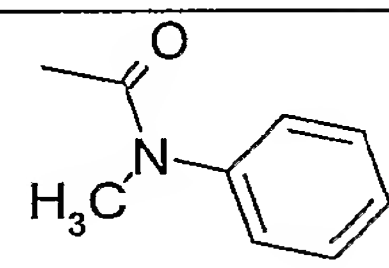
Examples 1116 – 1129

A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(2-amino-2-methylpropyl)-2-propyl-2*H*–pyrazolo[3,4-*c*]quinolin-4-amine (32 mg, 0.10 mmol, prepared as described in Example 64) and *N,N*-diisopropylethylamine (approximately 27 µL, 1.5 equivalents) in *N,N*-dimethylacetamide (1 mL). The test tubes were capped and shaken for about 4 hours. Two drops of water were added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85 . The table below shows the

reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
1116	None – starting material		298.2029
1117	Acetyl chloride		340.2144
1118	Benzoyl chloride		402.2336
1119	Hydrocinnamoyl chloride		430.2639
1120	Nicotinoyl chloride hydrochloride		403.2256
1121	*trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		442.2607
1122	Methanesulfonyl chloride		376.1814
1123	Dimethylsulfamoyl chloride		405.2071

1124	Benzenesulfonyl chloride		438.1994
1125	*alpha*-Toluenesulfonyl chloride		452.2145
1126	Isopropyl isocyanate		383.2566
1127	Cyclopropyl isothiocyanate		397.2189
1128	Phenyl isocyanate		417.2445
1129	*N*-Methyl-*N*-Phenylcarbamoyl chloride		431.2592

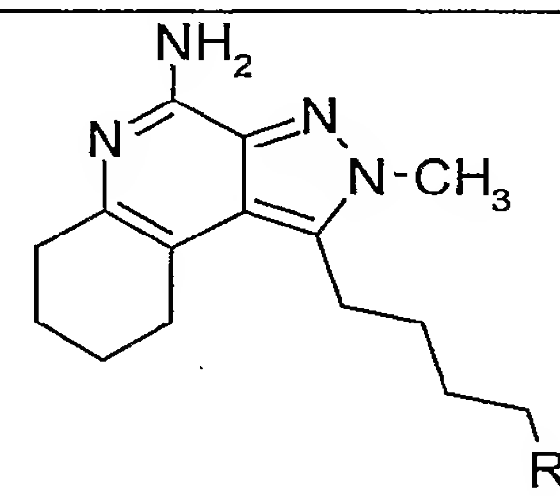
Examples 1130 – 1176

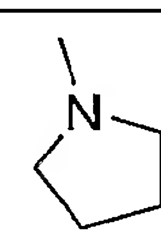
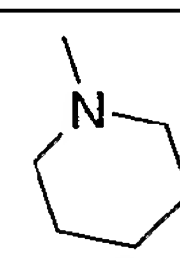
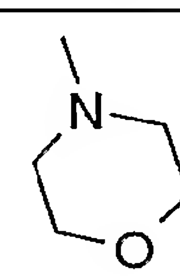
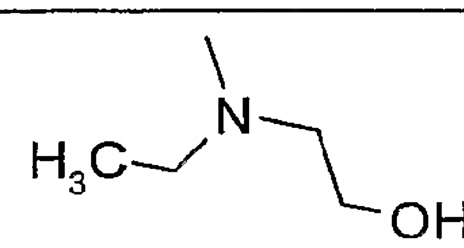
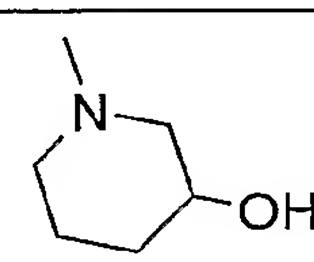
Part A

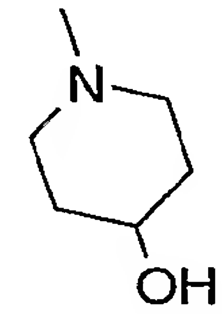
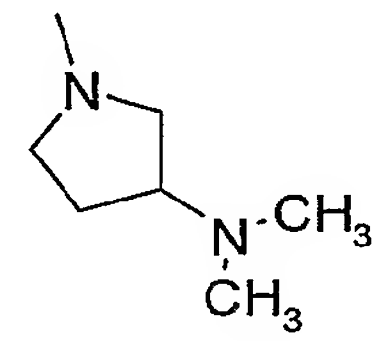
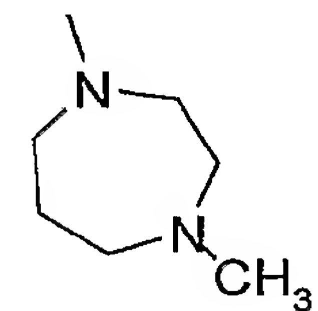
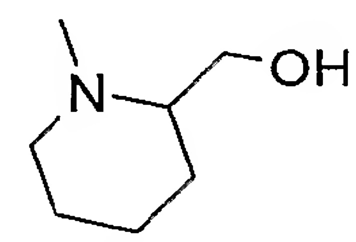
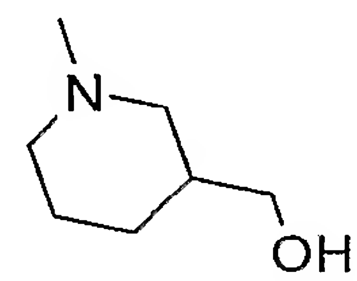
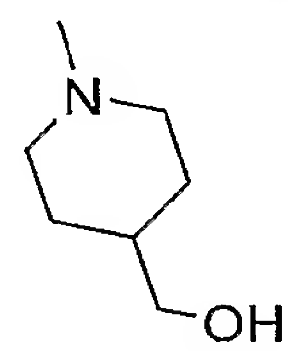
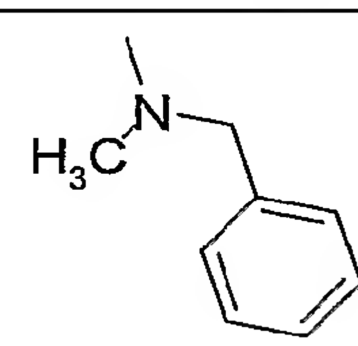
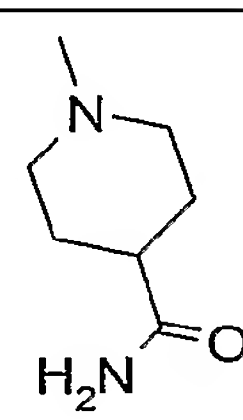
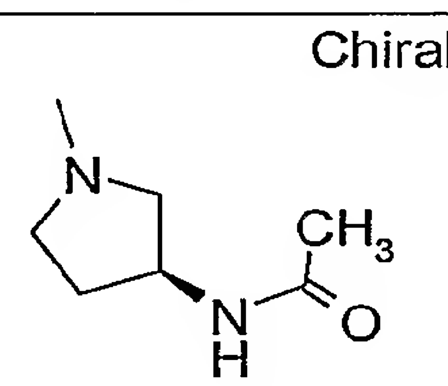
A mixture of 1-(4-chlorobutyl)-2-methyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine hydrochloride (2.8 g, prepared as described in Examples 454-488), platinum (IV) oxide (2.1 g), and trifluoroacetic acid (43 mL) was placed under hydrogen pressure (50 psi, 3.4 X 10^5 Pa) on a Parr shaker for 2 days. The reaction mixture was filtered through a layer of CELITE filter agent and the filter cake was rinsed with methanol. The filtrate was concentrated under reduced pressure. The residue was diluted with water (10 mL), made basic (pH 14) by the addition of 50% sodium hydroxide and then extracted with dichloromethane. The extract was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on a HORIZON HPFC system (40+M cartridge eluting with chloroform/CMA in a gradient from 100:0 to 80:20) to provide 2.0 g of 1-(4-chlorobutyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine as a light yellow solid.

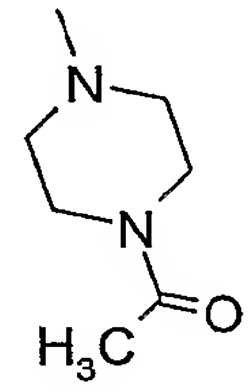
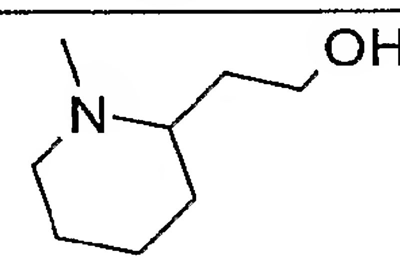
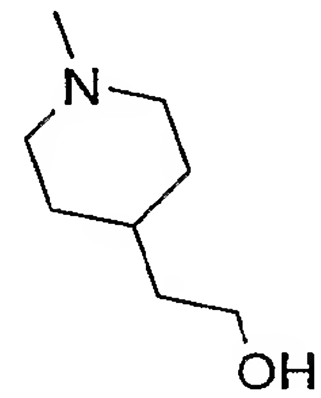
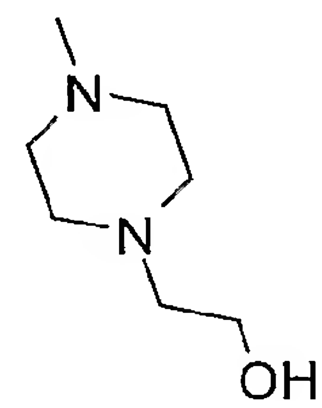
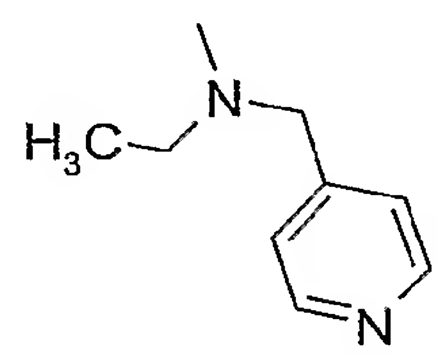
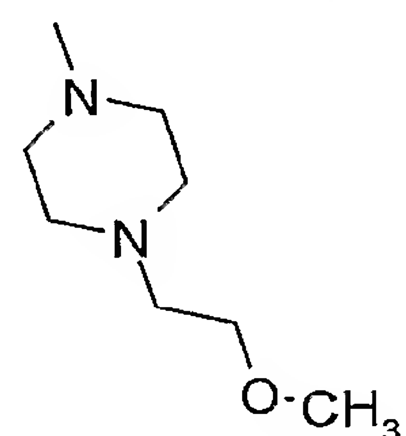
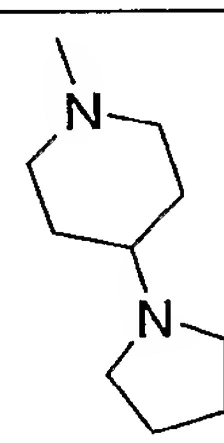
Part B

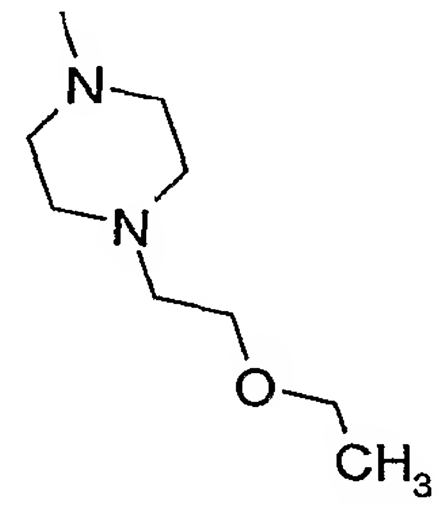
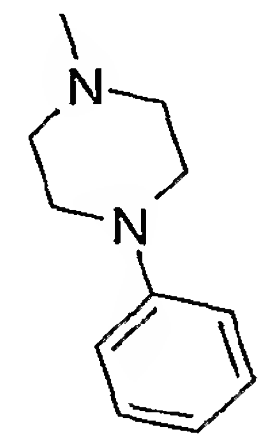
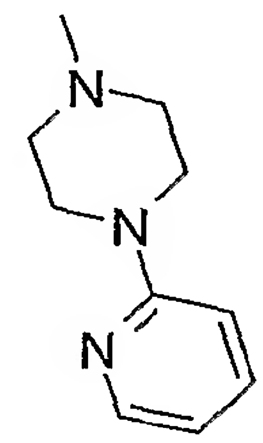
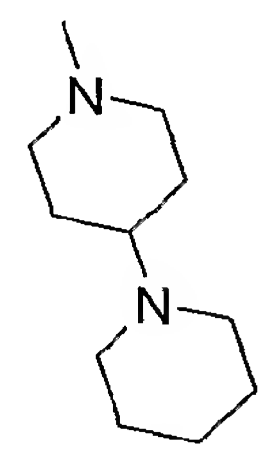
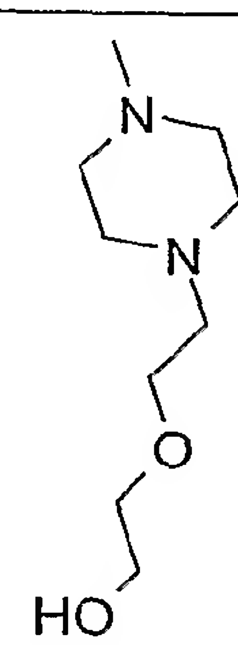
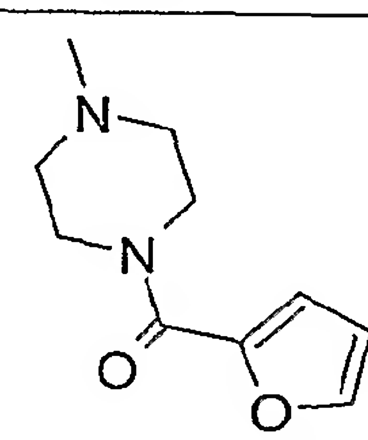
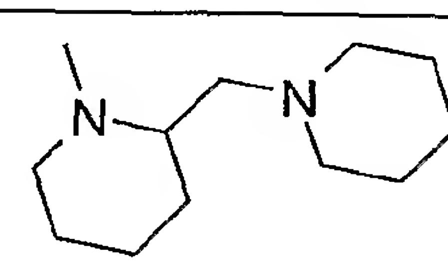
A reagent (0.15 mmol, 1.5 equivalents) from the table below was added to a test tube containing 1-(4-chlorobutyl)-2-methyl-6,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (29 mg, 0.10 mmol) and potassium carbonate (approximately 55 mg, 0.40 mmol) in *N,N*-dimethylacetamide (1 mL). The test tubes were capped and heated at 70 °C (amines) or 85 °C (phenols) for approximately 17 hours. The reaction mixtures were filtered and the solvent was removed from the filtrates by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

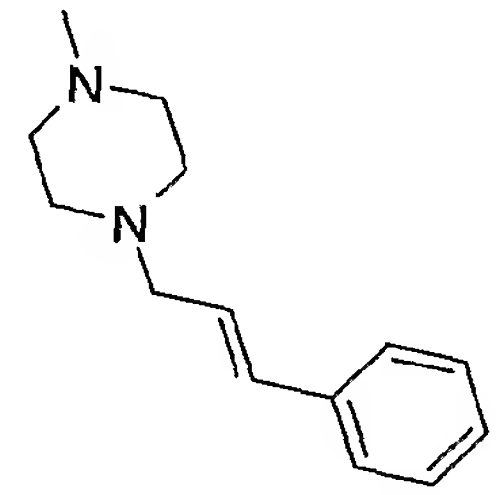
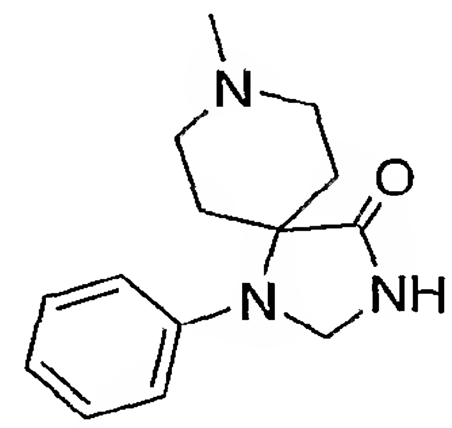
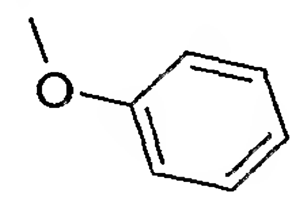
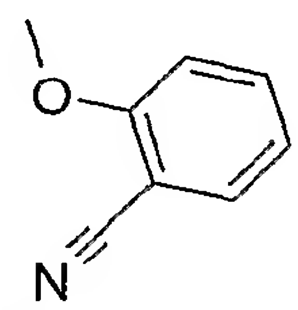
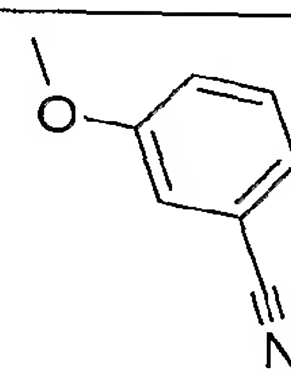
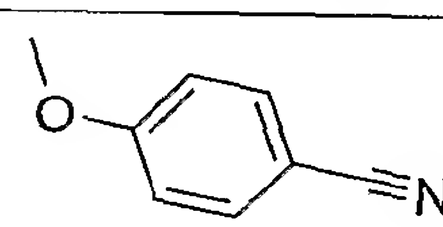
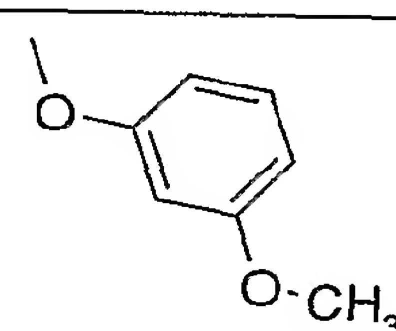
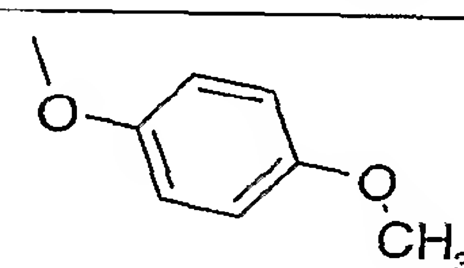
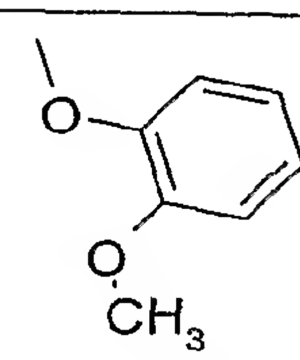


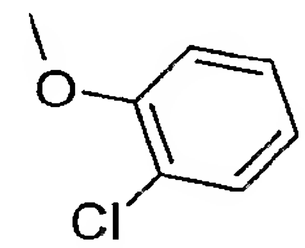
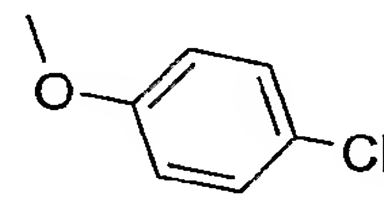
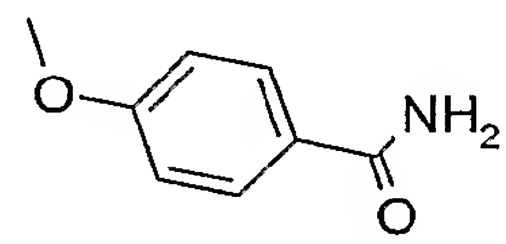
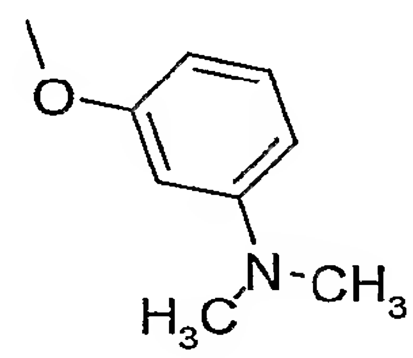
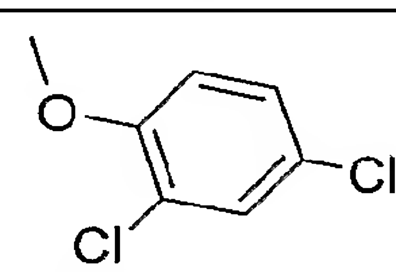
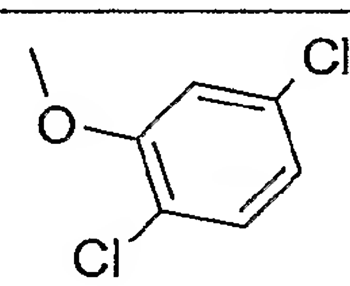
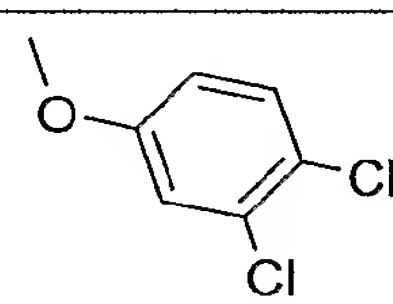
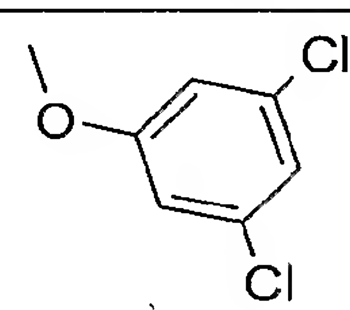
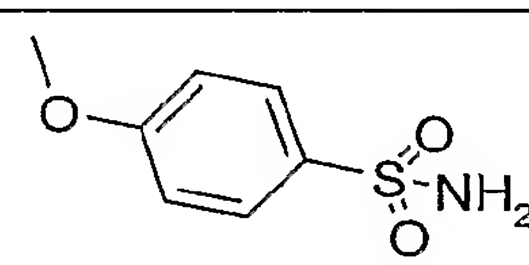
Example	Reagent	R	Measured Mass (M+H)
1130	None – starting material		293.1557
1131	Pyrrolidine		328.2524
1132	Piperidine		342.2643
1133	Morpholine		344.2464
1134	2-Ethylaminoethanol		346.2614
1135	3-Hydroxypiperidine		358.2613

1136	4-Hydroxypiperidine		358.2633
1137	3-(Dimethylamino)pyrrolidine		371.2914
1138	*N*-Methylhomopiperazine		371.2959
1139	2-Piperidinemethanol		372.2749
1140	3-(Hydroxymethyl)piperidine		372.2794
1141	4-(Hydroxymethyl)piperidine		372.2793
1142	*N*-Methylbenzylamine		378.2680
1143	Isonipecotamide		385.2697
1144	(3S)-(-)-3-Acetamidopyrrolidine		385.2710

1145	1-Acetylpiperazine		385.2723
1146	2-Piperidineethanol		386.2931
1147	4-Piperidineethanol		386.2928
1148	*N*-(2-Hydroxyethyl)piperazine		387.2910
1149	4-(Ethylaminomethyl)pyridine		393.2790
1150	1-(2-Methoxyethyl)piperazine		401.3011
1151	4-(1-Pyrrolidinyl)-piperidine		411.3260

1152	1-(2-Ethoxyethyl)piperazine		415.3208
1153	1-Phenylpiperazine		419.2944
1154	1-(2-Pyridyl)piperazine		420.2886
1155	4-Piperidinopiperidine		425.3397
1156	1-Hydroxyethylethoxypiperazine		431.3148
1157	1-(2-Furoyl)piperazine		437.2685
1158	2-Piperidin-1-ylmethyl-piperidine		439.3556

1159	1-Cinnamylpiperazine		459.3239
1160	1-Phenyl-1,3,8-triazospiro[4.5]decan-4-one		488.3132
1161	Phenol		351.2188
1162	2-Cyanophenol		376.2125
1163	3-Cyanophenol		376.2157
1164	4-Cyanophenol		376.2140
1165	3-Methoxyphenol		381.2270
1166	4-Methoxyphenol		381.2278
1167	Guaiacol		381.2270

1168	2-Chlorophenol		385.1785
1169	4-Chlorophenol		385.1780
1170	4-Hydroxybenzamide		394.2255
1171	3-Dimethylaminophenol		394.2589
1172	2,4-Dichlorophenol		419.1378
1173	2,5-Dichlorophenol		419.1363
1174	3,4-Dichlorophenol		419.1374
1175	3,5-Dichlorophenol		419.1381
1176	4-Hydroxybenzenesulfonamide		430.1886

Examples 1177 – 1191

Part A

DMF (50 mL) was added to a mixture of 1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (3 g, 12.5 mmol, prepared as described in Example 9), 4-bromobutylphthalimide (3.9 g, 13.7 mmol), and potassium carbonate (5.2 g, 37.5 mmol).

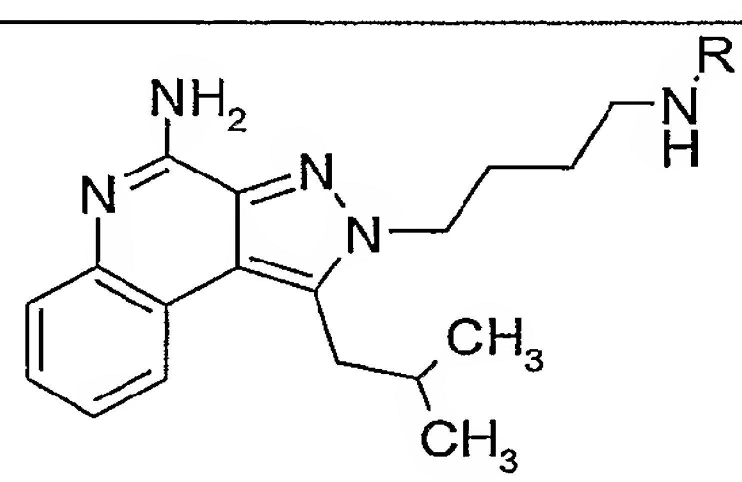
The reaction mixture was heated at 60 °C with stirring under a nitrogen atmosphere for about 18 hours. The reaction mixture was filtered to remove excess potassium carbonate. The filtrate was diluted with water and then extracted with ethyl acetate. The extract was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on a HORIZON HPFC system (silica gel, eluting first with ethyl acetate and then with a gradient of methanol in ethyl acetate) to provide 2.0 g of 2-{4-[4-amino-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-2-yl]butyl}-1*H*-isoindole-1,3(2*H*)-dione.

Part B

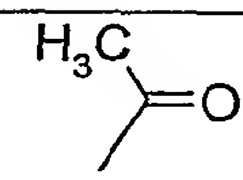
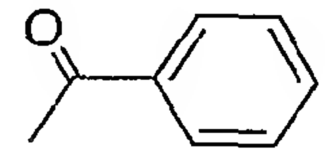
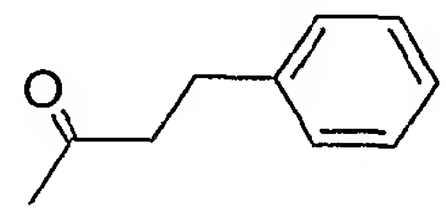
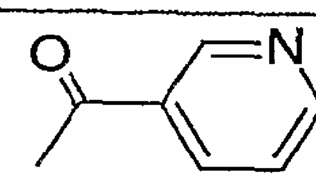
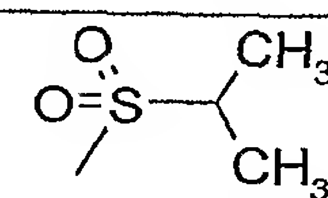
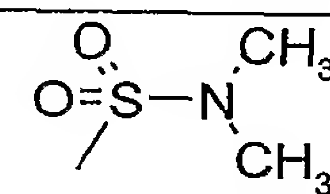
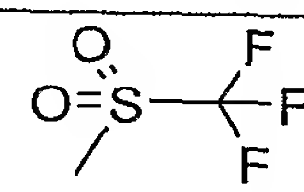
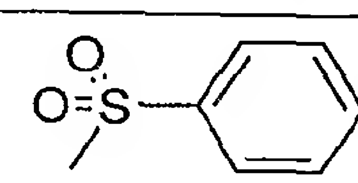
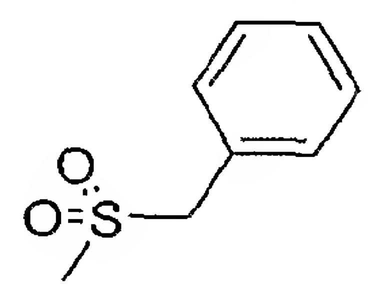
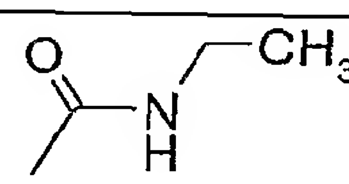
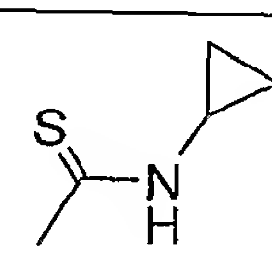
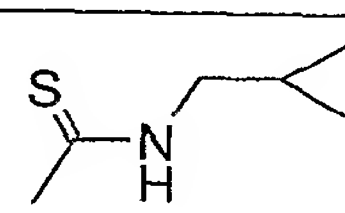
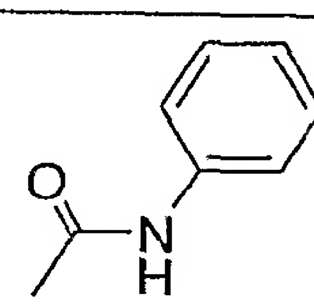
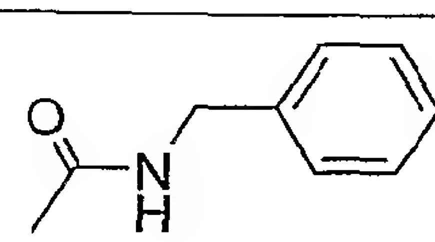
The material from Part A was combined with hydrazine monohydrate (1.1 mL. 5 eq) and ethanol (100 mL). The reaction mixture was heated at reflux for 2 hours and then allowed to cool to ambient temperature overnight. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to provide 0.8 g of 2-(4-aminobutyl)-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine.

Part C

A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 2-(4-aminobutyl)-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (31 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (approximately 35 µL, 2 equivalents) in *N,N*-dimethylacetamide (1 mL). The test tubes were capped and shaken for about 16 hours. Two drops of water were added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

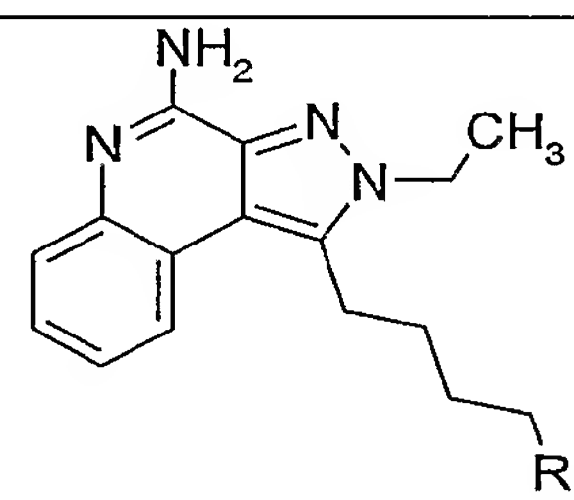


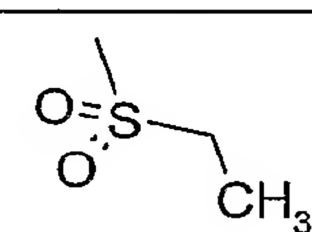
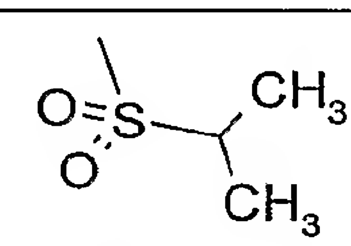
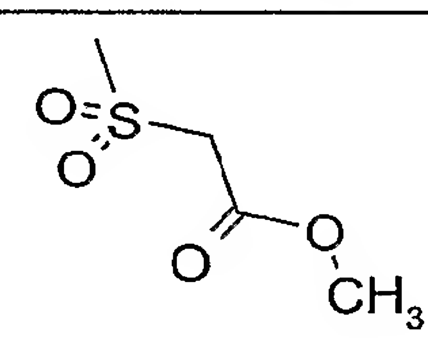
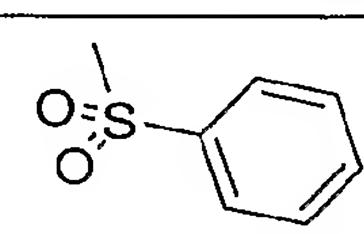
Example	Reagent	R	Measured Mass (M+H)
1177	None – starting material	H	312.2203

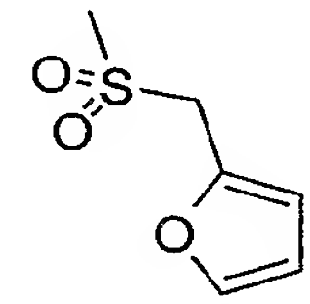
1178	Acetyl chloride		354.2316
1179	Benzoyl chloride		416.2444
1180	Hydrocinnamoyl chloride		444.2769
1181	Nicotinoyl chloride hydrochloride		417.2406
1182	Isopropylsulfonyl chloride		418.2296
1183	Dimethylsulfamoyl chloride		419.2213
1184	Trifluoromethanesulfonyl chloride		444.1689
1185	Benzenesulfonyl chloride		452.2150
1186	*alpha*-Toluenesulfonyl chloride		466.2242
1187	Ethyl isocyanate		383.2586
1188	Cyclopropyl isothiocyanate		411.2358
1189	Cyclopropylmethyl isothiocyanate		425.2496
1190	Phenyl isocyanate		431.2590
1191	Benzyl isocyanate		445.2752

Examples 1192 – 1197

A reagent (0.12 mmol, 1.2 equivalents) from the table below and a solution of potassium *tert*-butoxide (150 µL of 1 M in THF, 1.5 eq) were added to a test tube containing 1-(4-chlorobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine (30 mg, 0.10 mmol) in DMF (1 mL). The tubes were capped and stirred (magnetic stir bar) at ambient temperature for about 65 hours. Aqueous hydrochloric acid (300 µL of 1 N) and peracetic acid (57 µL of 32 wt %) were added to each tube; then stirring was continued for an additional 3 hours. The solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
1192	None – starting material		303.1352
1193	Ethanethiol		361.1699
1194	2-Propanethiol		375.1861
1195	Methyl thioglycolate		405.1585
1196	Thiophenol		409.1690

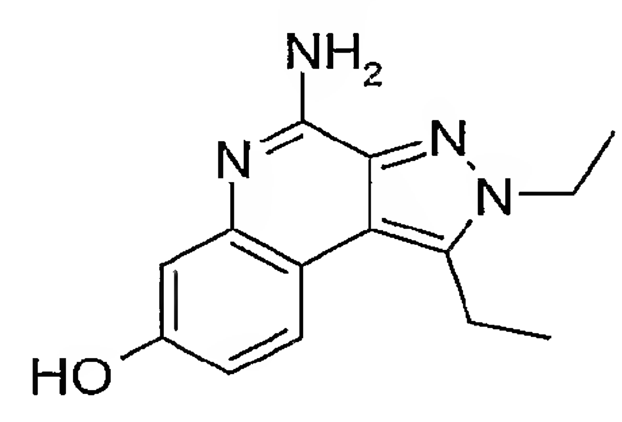
1197	Furfuryl mercaptan		413.1659

Example 1198

Under a nitrogen atmosphere, potassium *tert*-butoxide (218 µL of 1 M in THF, 1.5 eq) was added to a solution of 1-(4-chlorobutyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinoline-4-amine (44 mg, 0.145 mmol) and butanethiol (19 µL, 0.174 mmol) in DMF (1.5 mL). The reaction mixture was stirred at ambient temperature overnight. Peracetic acid (76 µL of 32 wt %) was added and the reaction mixture was stirred for 2 hours. The reaction mixture was acidified (pH 3) by the addition of 1 N hydrochloric acid and then loaded onto a solid phase extraction cartridge (Waters, MCX 6cc). The reaction mixture was pushed through the cartridge with light nitrogen pressure to provide fraction 1. The cartridge was eluted sequentially with methanol (5 mL) and ammonia/methanol (5 mL of 1 N) to provide fractions 2 and 3 respectively. The solvent was removed by vacuum centrifugation to provide 1-[4-(butylsulfonyl)butyl]-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine, measured mass (M + H): 389.1989.

Example 1199

4-Amino-1,2-diethyl-2*H*-pyrazolo[3,4-*c*]quinolin-7-ol

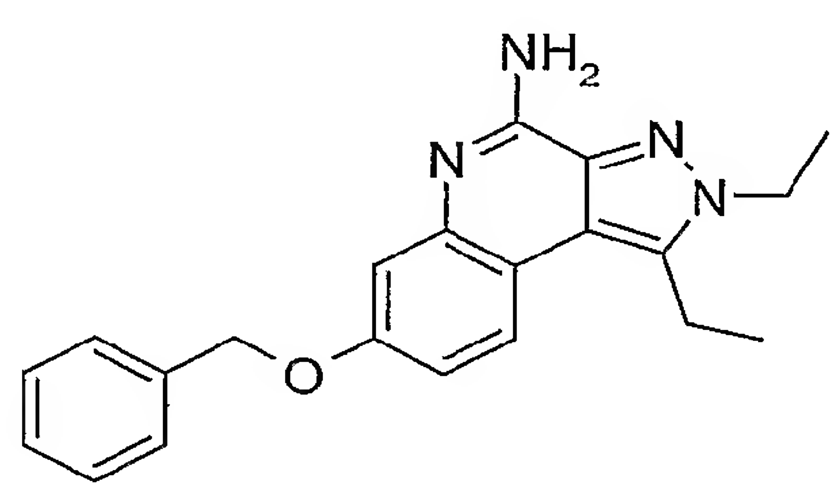


Dichloromethane (1 mL) was added to a vial containing 1,2-diethyl-7-methoxy-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (20 mg, 0.074 mmol, prepared as described in Example 573). The reaction mixture was stirred at 0 °C for 5 minutes. Cold boron tribromide (370 µL of 1 M in dichloromethane, 0.37 mmol) was added dropwise and the reaction mixture

was stirred at 0 °C for 20 minutes. The ice bath was removed and the reaction mixture was stirred for about 3 hours. The solvent was evaporated. The residue was combined with methanol (2 mL) and 6 N hydrochloric acid (500 µL); and then stirred for 1 hour. The mixture was made basic by the addition of 6 M sodium hydroxide and a portion of the solvent was evaporated. The residue was partitioned between dichloromethane (25 mL) and water (25 mL). The layers were separated. The aqueous layer was evaporated to provide a yellow solid. The solid was suspended in methanol. The methanol was evaporated and the residue was purified as described in Examples 71-85 to provide the trifluoroacetate salt of 4-amino-1,2-diethyl-2*H*-pyrazolo[3,4-*c*]quinolin-7-ol, measured mass (M + H): 257.1408.

Example 1200

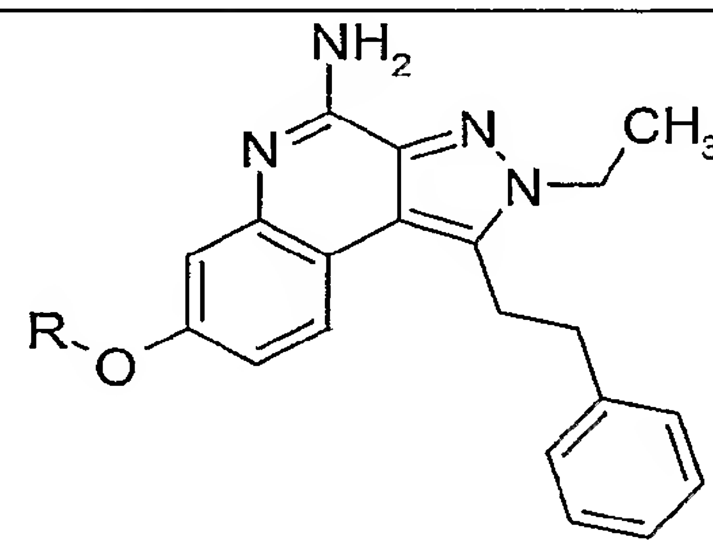
7-(Benzyloxy)-1,2-diethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine

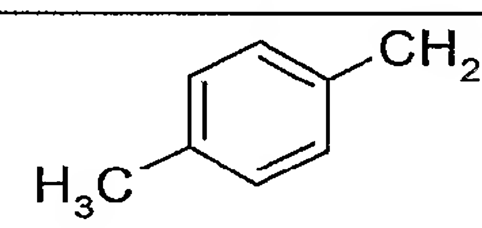
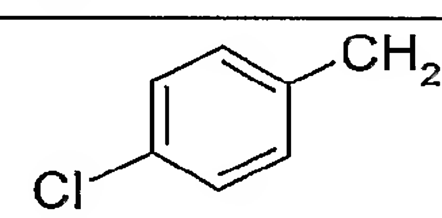


Chloroform (2 mL) and cesium carbonate (32.6 mg, 0.1 mmol) were added to a vial containing 4-amino-1,2-diethyl-2*H*-pyrazolo[3,4-*c*]quinolin-7-ol (17 mg, 0.05 mmol) and the mixture was stirred at ambient temperature for 5 minutes. Benzyl bromide (6.54 µL, 0.055 mmol) was added and the reaction mixture was stirred at 50 °C for 30 minutes. Analysis by LCMS indicated that only a small amount of product had formed. The chloroform was evaporated and the residue was dissolved in *N,N*-dimethylacetamide. The reaction mixture was stirred at 50 °C for about 1 hour. The solvent was evaporated and the residue was purified as described in Examples 71-85 to provide the trifluoroacetate salt of 7-(benzyloxy)-1,2-diethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine, measured mass (M + H): 423.2190.

Examples 1201 & 1202

N,N-Dimethylacetamide (2 mL) and cesium carbonate (32.6 mg, 0.1 mmol) were added to vials containing 4-amino-1,2-diethyl-2*H*-pyrazolo[3,4-*c*]quinolin-7-ol (17 mg, 0.05 mmol) and the mixture was stirred at ambient temperature for 5 minutes. A reagent (6.54 µL, 0.055 mmol) from the table below was added to a vial and the reaction mixture was stirred at 50 °C for 4 hours. The solvent was evaporated and the residue was purified as described in Examples 71-85. The table below shows the reagents used, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

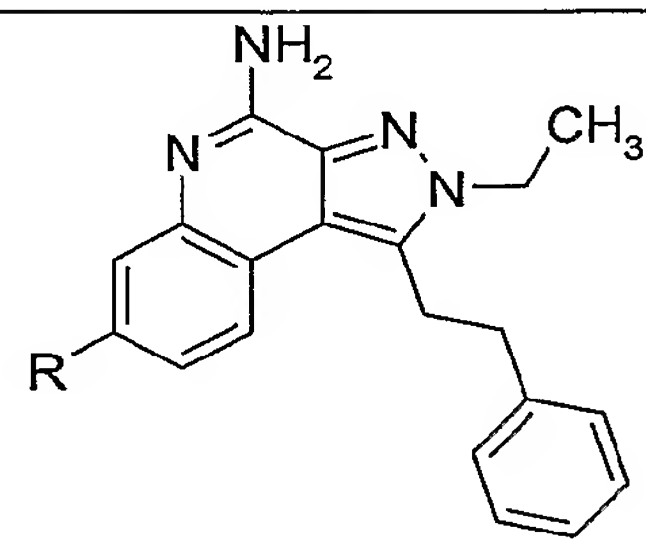


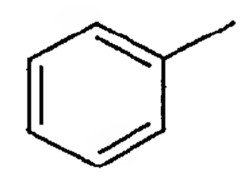
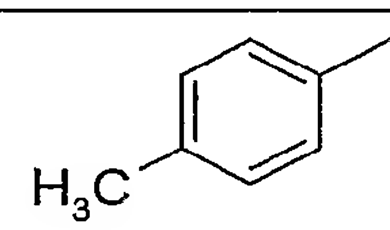
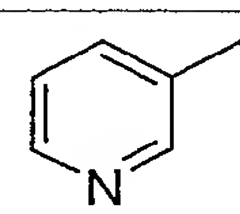
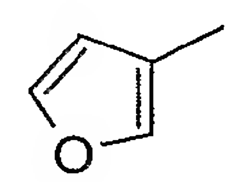
Example	Reagent	R	Measured Mass (M + H)
1201	*alpha*-Bromo-*p*-xylene		437.2349
1202	4-Chlorobenzyl bromide		457.1809

Examples 1203 - 1206

A boronic acid (2.1 eq, 0.11 mmol) from the table below and *n*-propyl alcohol (720 µL) were added to a vial containing 4-amino-2-ethyl-1-(2-phenylethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-7-yl trifluoromethanesulfonate (23 mg, 0.05 mmol, prepared as described in Example 576). The vial was purged with nitrogen. Palladium (II) acetate (1.12 mg, 10 mole %), 2 M aqueous sodium carbonate (250 µL), water (50 µL), and triphenylphosphine (2.6 mg (20 mole %) in 100 µL of *n*-propyl alcohol) were sequentially added. The reaction mixture was heated at 80 °C with stirring for 1 hour, allowed to cool to ambient temperature, and then filtered through a plug of glass wool. The plug was washed with *n*-propyl alcohol, methanol, and dichloromethane. The filtrate was evaporated and the

residue was purified as described in Examples 71-85. The table below shows the reagents used, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
1203	Phenylboronic acid		393.2108
1204	4-Methylphenylboronic acid		407.2201
1205	Pyridine-3-boronic acid		394.2031
1206	Furan-3-boronic acid		383.1852

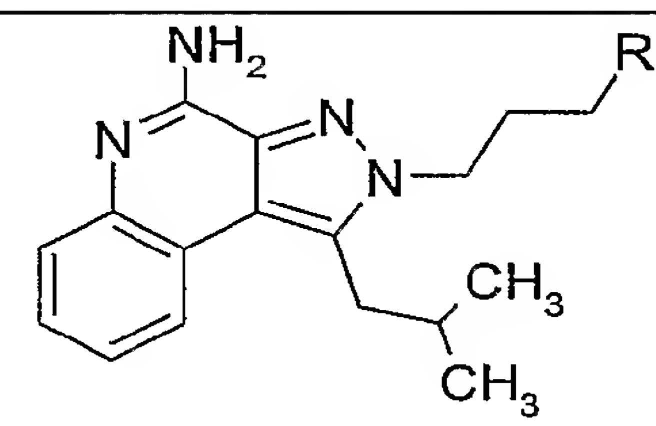
Examples 1207 – 1216

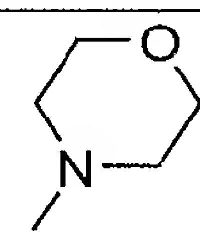
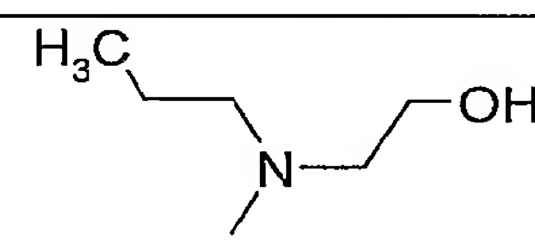
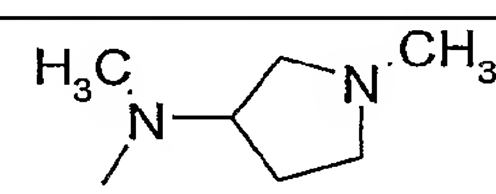
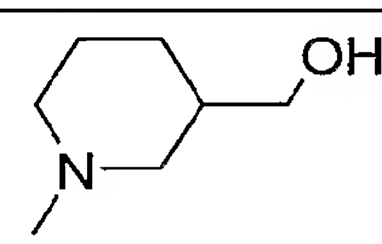
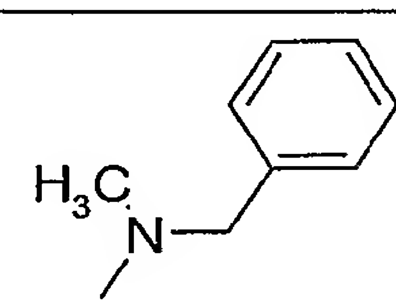
Part A

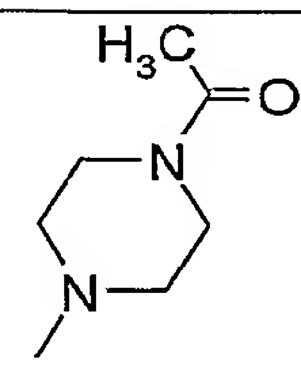
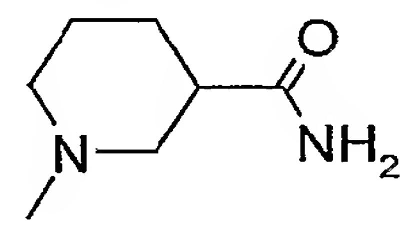
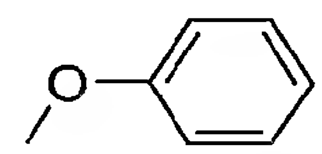
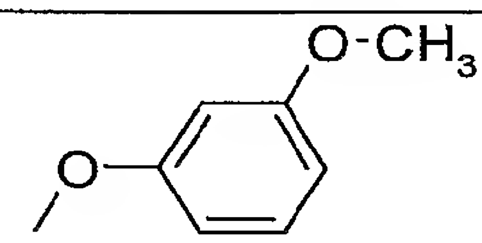
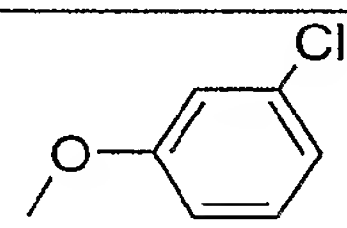
1-(2-Methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (2.4 g, 9.99 mmol, prepared as described in Example 9), potassium carbonate (5.5 g, 39.9 mmol), 3-chloroiodopropane (1.2 mL, 11.0 mmol), and DMF (110 mL) were combined and heated at 40 °C overnight. The reaction mixture was diluted with water and then extracted with ethyl acetate. The combined extracts were washed with water and concentrated under reduced pressure. The residue was purified twice by chromatography on a HORIZON HPFC system (silica gel eluting with ethyl acetate) to provide 2-(3-chloropropyl)-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine.

Part B

A reagent (0.15 mmol, 1.5 equivalents) from the table below was added to a test tube containing 2-(3-chloropropyl)-1-(2-methylpropyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (32 mg, 0.10 mmol) and potassium carbonate (approximately 55 mg, 0.40 mmol) in *N,N*-dimethylacetamide (1 mL). The test tubes were capped and heated at 70 °C (amines) or 85 °C (phenols) for approximately 18 hours. The reaction mixtures were filtered and the solvent was removed from the filtrates by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
1207	Morpholine		368.2472
1208	2-(Propylamino)ethanol		384.2784
1209	*N,N'*-Dimethyl-3-aminopyrrolidine		395.2943
1210	3-(Hydroxymethyl)piperidine		396.2797
1211	*N*-Methylbenzylamine		402.2664

1212	1-Acetylpiperazine		409.2721
1213	Nipecotamide		409.2733
1214	Phenol		375.2200
1215	3-Methoxyphenol		405.2329
1216	3-Chlorophenol		409.1805

Examples 1217 – 1241

Part A

A mixture of 2-*tert*-butoxycarbonylamino-3-pyridylboronic acid (11.37 g, 47.78 mmol, prepared as described in Example 15), *n*-propanol (80 mL), and 1 M hydrochloric acid (60 mL) was heated in an oil bath at 80 °C for 1 hour and then allowed to cool to ambient temperature. Solid sodium carbonate was added with stirring to neutralize the hydrochloric acid and to serve as a base in the next step.

Part B

tert-Butyl 2-(4-bromo-3-cyano-1-propyl-1*H*-pyrazol-5-yl)ethylcarbamate (11.36 g, 31.84 mmol, prepared as described in Example 51), *n*-propanol (20 mL), and palladium (II) acetate (143 mg, 0.64 mmol) were added to the mixture from Part A. The reaction mixture was degassed and backfilled with nitrogen three times and then heated at 100 °C for 2 days. The reaction mixture was allowed to cool to ambient temperature and the *n*-propanol was removed under reduced pressure. The residue was diluted with chloroform (250 mL), washed with water (2 x 100 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide a light yellow solid. This material was purified by chromatography on a HORIZON HPFC system (silica gel eluting with a

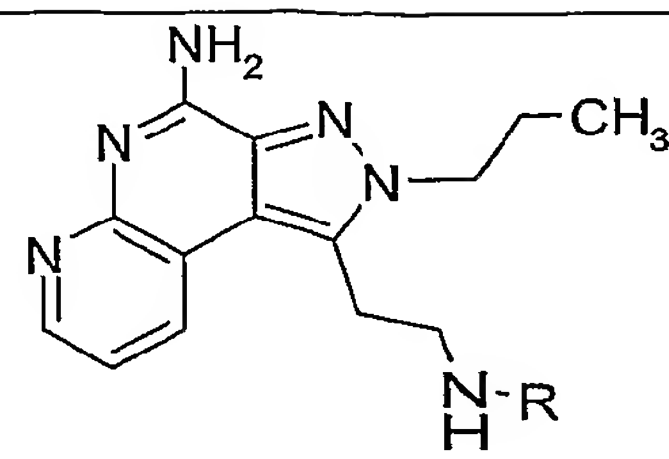
gradient of 0 – 45% of 80:20 CMA:chloroform in chloroform) to provide 2.47 g of a light yellow solid. This material was suspended in acetonitrile (25 mL), sonicated for about 15 seconds, isolated by filtration, rinsed with acetonitrile, and dried to provide 2.25 g of *tert*-butyl 2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]-1,8-naphthyridin-1-yl)ethylcarbamate as a white solid.

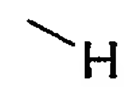
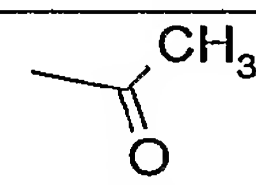
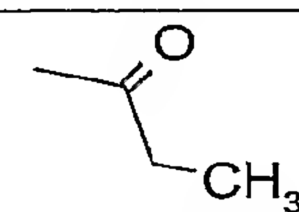
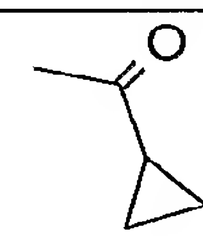
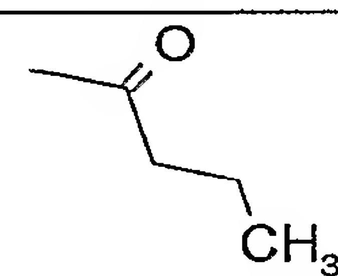
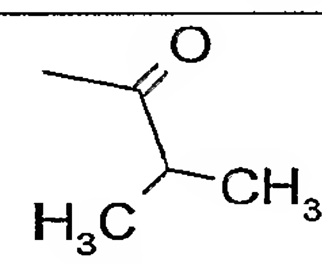
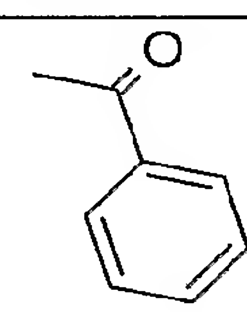
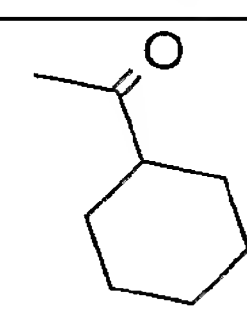
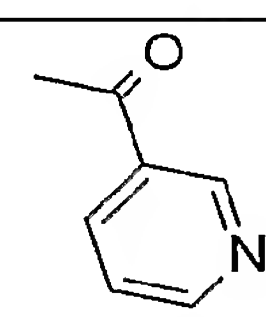
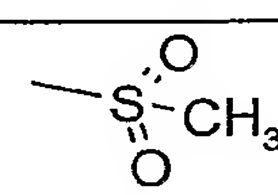
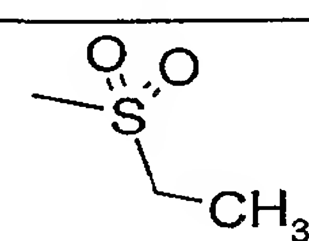
Part C

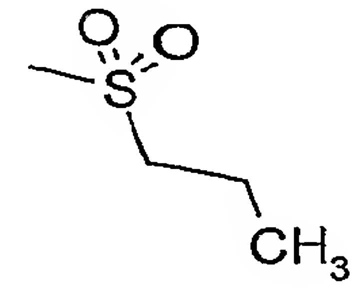
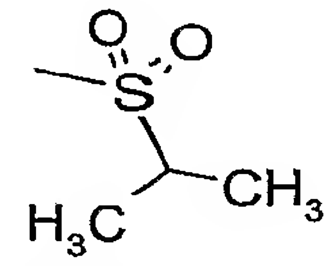
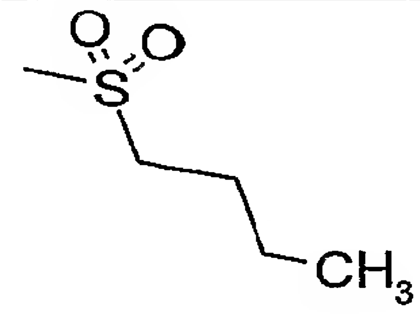
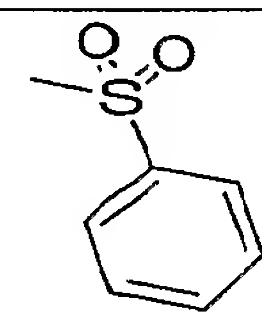
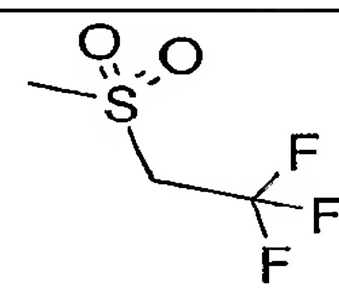
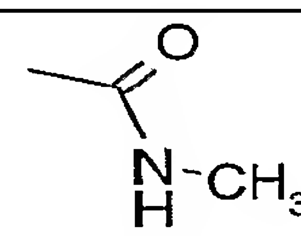
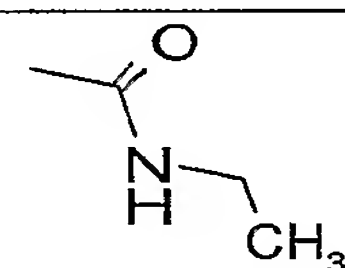
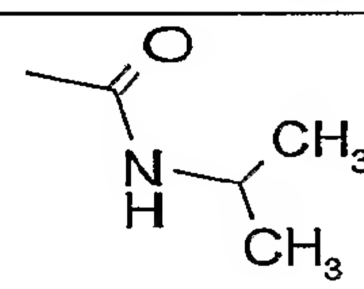
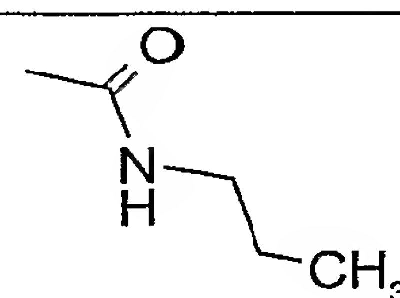
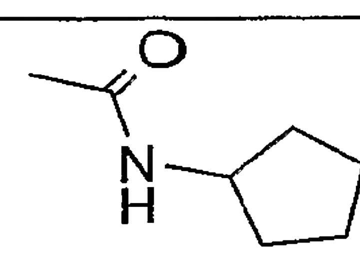
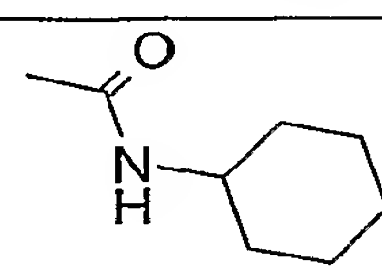
Hydrochloric acid (3 mL of 2.7 M in ethanol) was added to a suspension of *tert*-butyl 2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]-1,8-naphthyridin-1-yl)ethylcarbamate (0.52 g) in ethanol (10 mL). The mixture was heated at 80 °C for about 1 hour and then concentrated under reduced pressure. The residue was partitioned between water (50 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was made basic with ammonium hydroxide and then extracted with dichloromethane (2 x 50 mL). The combined organics were washed with brine (1 x 50 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 0.29 g of crude product as a white solid. The reaction was repeated using 2.05 g of starting material to provide 1.18 g of crude product as a white solid. The two lots were combined and purified by chromatography on a HORIZON HPFC system (silica gel eluting with a gradient of 20 – 60% of 80:20 CMA:chloroform in chloroform) to provide 0.48 g of 1-(2-aminoethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]-1,8-naphthyridin-4-amine as a white solid.

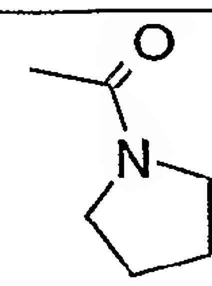
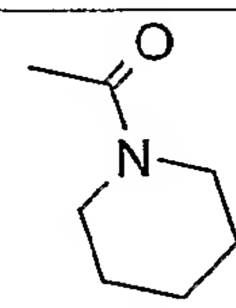
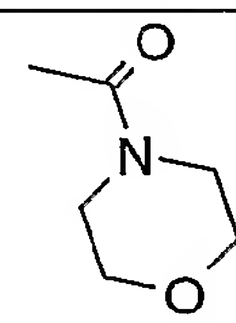
Part D

A reagent (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing 1-(2-aminoethyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]-1,8-naphthyridin-4-amine (26 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (approximately 36 µL, 2 equivalents) in chloroform (2 mL). The test tubes were capped and shaken for about 4 hours. Two drops of water were added to each test tube, and the solvent was removed by vacuum centrifugation. The compounds were purified as described in Examples 71-85. The table below shows the reagent added to each test tube, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



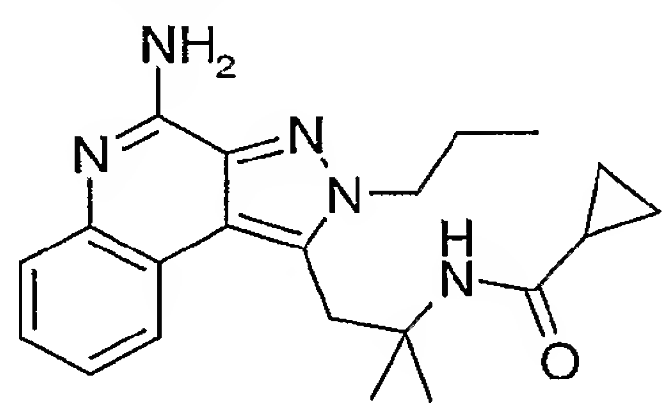
Example	Reagent	R	Measured Mass (M+H)
1217	None – starting material only		271.1696
1218	Acetyl chloride		313.1781
1219	Propionyl chloride		327.1962
1220	Cyclopropanecarbonyl chloride		339.1948
1221	Butyryl chloride		341.2108
1222	Isobutyryl chloride		341.2107
1223	Benzoyl chloride		375.1966
1224	Cyclohexanecarbonyl chloride		381.2433
1225	Nicotinoyl chloride hydrochloride		376.1888
1226	Methanesulfonyl chloride		349.1472
1227	Ethanesulfonyl chloride		363.1638

1228	1-Propanesulfonyl chloride		377.1736
1229	Isopropylsulfonyl chloride		377.1794
1230	1-Butanesulfonyl chloride		391.1938
1231	Benzenesulfonyl chloride		411.1636
1232	2,2,2-Trifluoroethanesulfonyl chloride		417.1358
1233	Methyl isocyanate		328.1909
1234	Ethyl isocyanate		342.2059
1235	Isopropyl isocyanate		356.2222
1236	*N*-Propyl isocyanate		356.2213
1237	Cyclopentyl isocyanate		382.2394
1238	Cyclohexyl isocyanate		396.2547

1239	1-Pyrrolidinecarbonyl chloride		368.2217
1240	1-Piperidinecarbonyl chloride		382.2379
1241	4-Morpholinecarobonyl chloride		384.2181

Example 1242

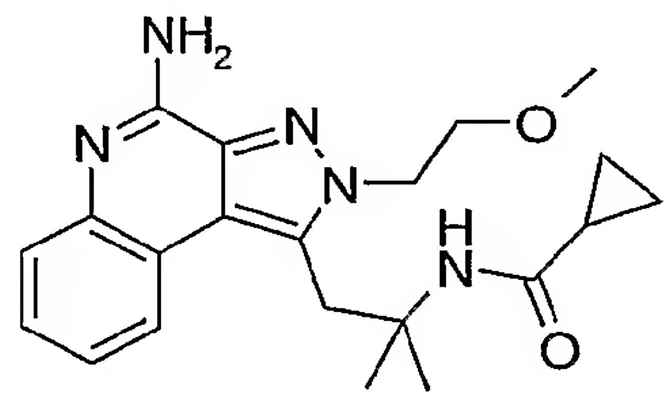
N-[2-(4-Amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]cyclopropylamide



The method described in Example 65 can be used to treat 1-(2-amino-2-methylpropyl)-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 64) with cyclopropanecarbonyl chloride in lieu of acetyl chloride to provide *N*-[2-(4-amino-2-propyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]cyclopropylamide.

Example 1243

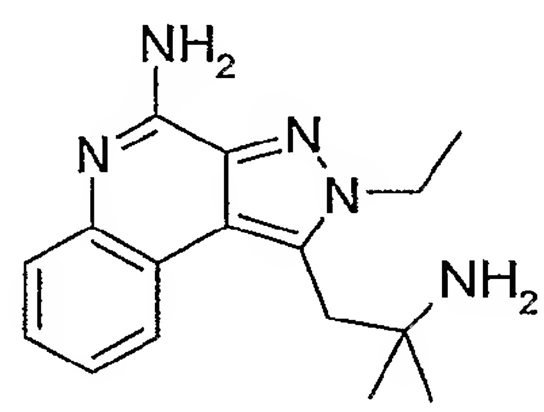
N-{2-[4-Amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}cyclopropylamide



The method described in Example 65 can be used to treat 1-(2-amino-2-methylpropyl)-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine (prepared as described in Example 590) with cyclopropanecarbonyl chloride in lieu of acetyl chloride to provide *N*-{2-[4-amino-2-(2-methoxyethyl)-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl]-1,1-dimethylethyl}cyclopropylamide.

Example 1244

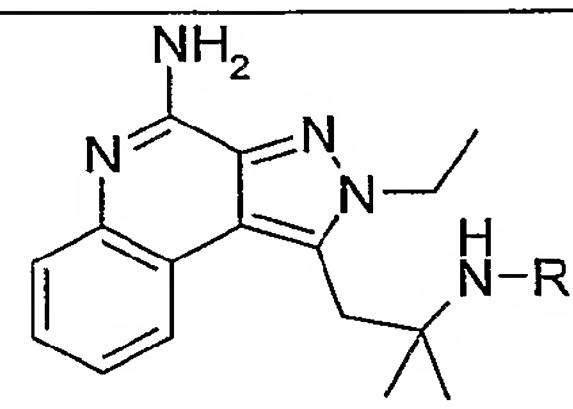
1-(2-Amino-2-methylpropyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine

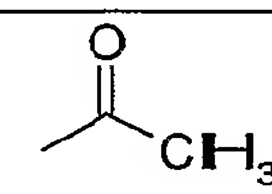
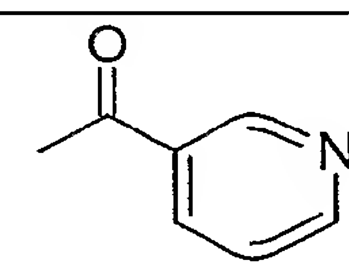
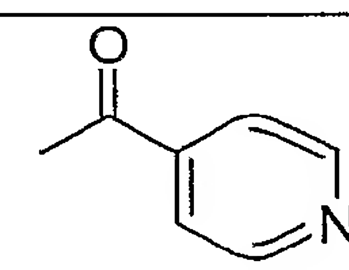
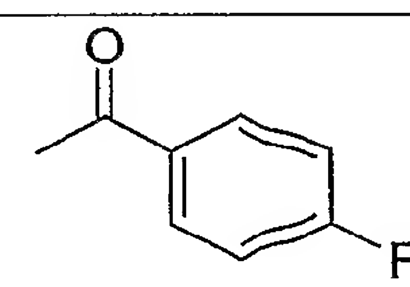
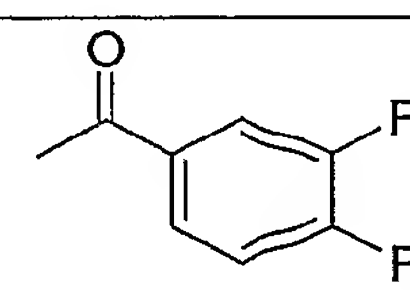
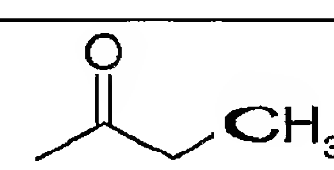


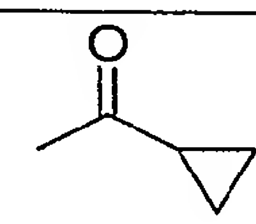
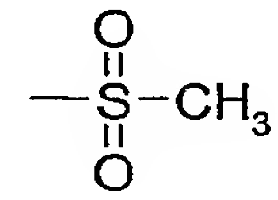
The methods described in Parts A through G of Example 64 can be used to prepare 1-(2-amino-2-methylpropyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine, with ethylhydrazine oxalate used in lieu of propylhydrazine oxalate in Part A.

Examples 1245 – 1252

The method described in Example 65 can be used to treat 1-(2-amino-2-methylpropyl)-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-4-amine with the acid chlorides or sulfonyl chloride shown in the following table to provide the compounds shown in the following table.

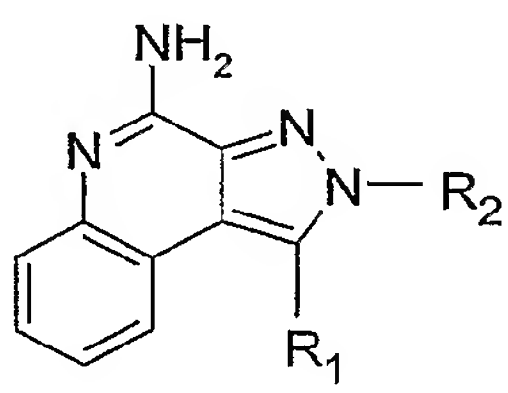


Example	Reagent	Name	R
1245	Acetyl chloride	*N*-[2-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]acetamide	
1246	Nicotinoyl chloride hydrochloride	*N*-[2-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]nicotinamide	
1247	Isonicotinoyl chloride hydrochloride	*N*-[2-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]isonicotinamide	
1248	4-Fluorobenzoyl chloride	*N*-[2-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]-4-fluorobenzamide	
1249	3,4-Difluorobenzoyl chloride	*N*-[2-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]-3,4-difluorobenzamide	
1250	Propionyl chloride	*N*-[2-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]propionamide	

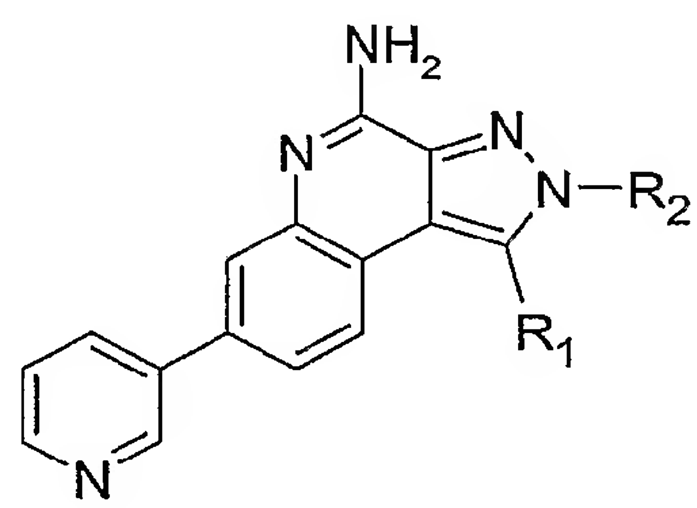
1251	Cyclopropanecarbonyl chloride	*N*-[2-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]cyclopropylamide	
1252	Methanesulfonyl chloride	*N*-[2-(4-Amino-2-ethyl-2*H*-pyrazolo[3,4-*c*]quinolin-1-yl)-1,1-dimethylethyl]methanesulfonamide	

Exemplary Compounds

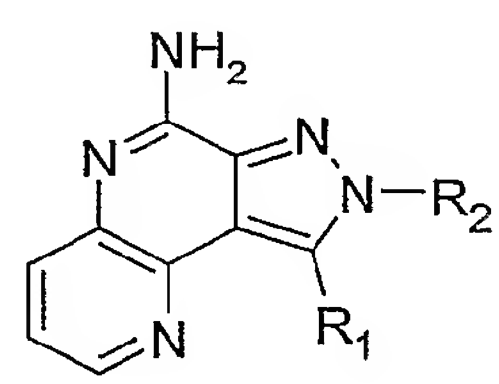
Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IIIa, IIIb, IVa, VIa, VIIa, VIIIa, or IXa) and the following R_1, and R_2 substituents, wherein each line of the table represents a specific compound.



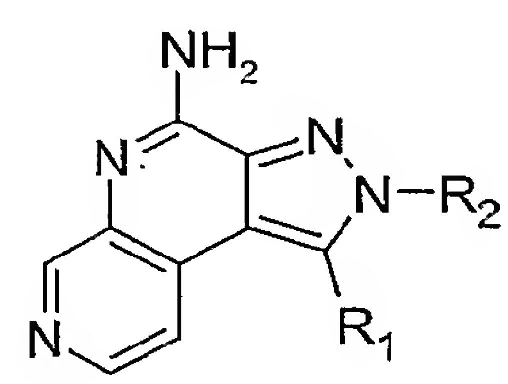
IIIa



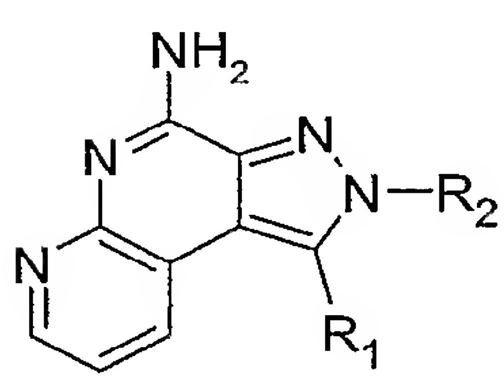
IIIb



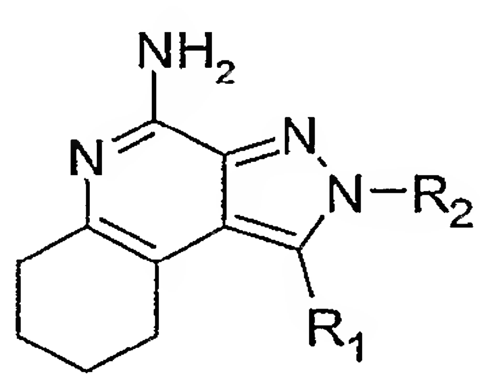
IVa



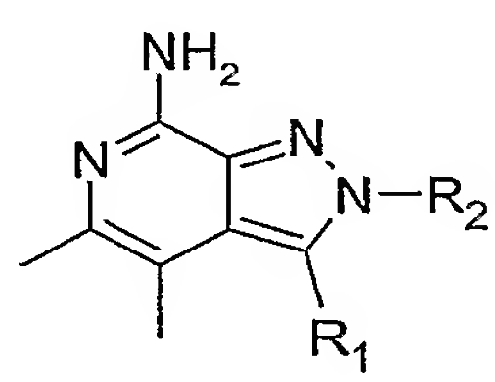
VIa



VIIa



VIIIa



IXa

R_1	R_2
methyl	hydrogen
methyl	methyl
methyl	ethyl
methyl	n-propyl
methyl	n-butyl
methyl	benzyl
methyl	2-methoxyethyl
methyl	2-hydroxyethyl

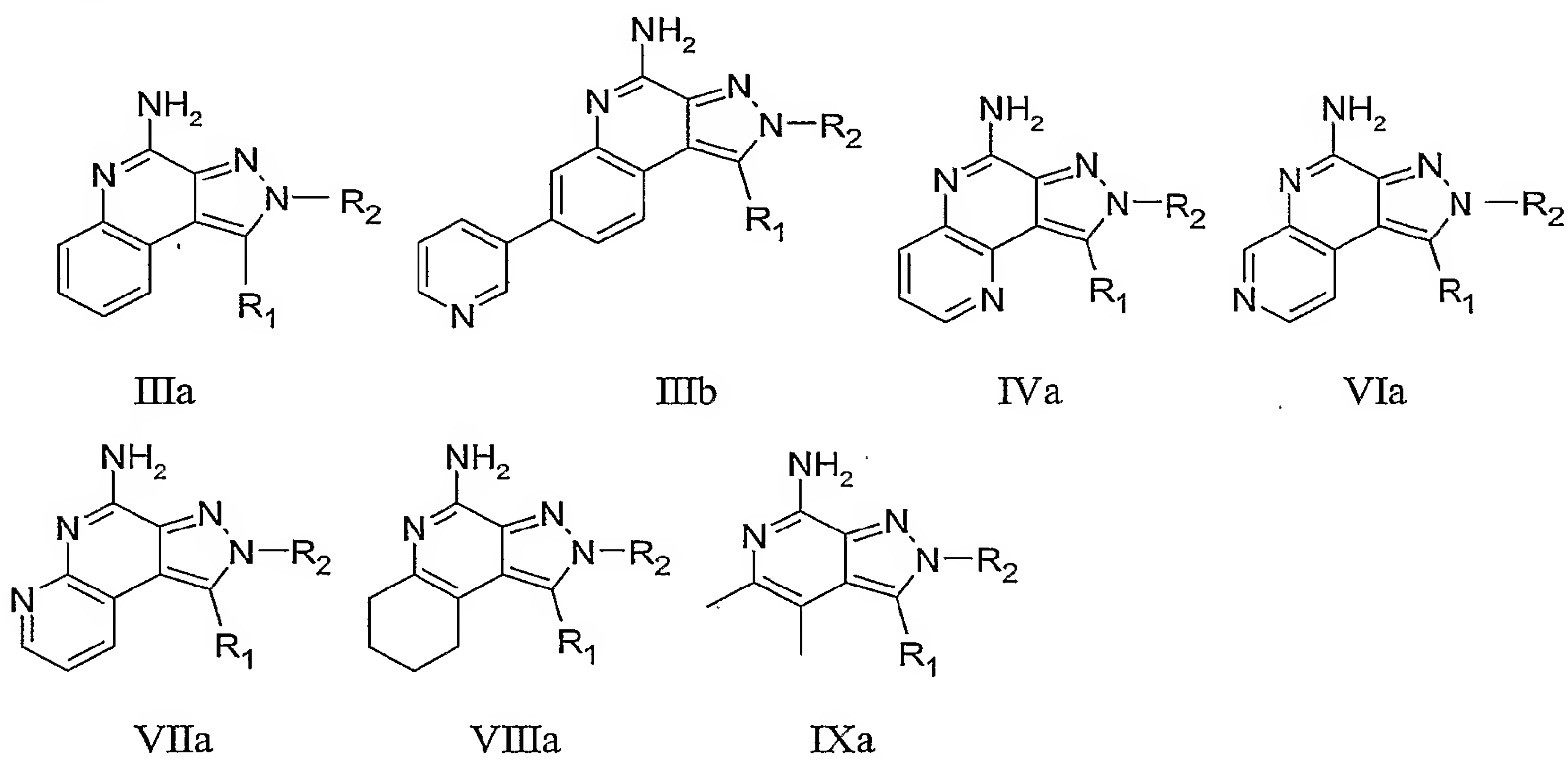
ethyl	hydrogen
ethyl	methyl
ethyl	ethyl
ethyl	n-propyl
ethyl	n-butyl
ethyl	benzyl
ethyl	2-methoxyethyl
ethyl	2-hydroxyethyl
2-methylpropyl	hydrogen
2-methylpropyl	methyl
2-methylpropyl	ethyl
2-methylpropyl	n-propyl
2-methylpropyl	n-butyl
2-methylpropyl	benzyl
2-methylpropyl	2-methoxyethyl
2-methylpropyl	2-hydroxyethyl
2-methanesulfonylethyl	hydrogen
2-methanesulfonylethyl	methyl
2-methanesulfonylethyl	ethyl
2-methanesulfonylethyl	n-propyl
2-methanesulfonylethyl	n-butyl
2-methanesulfonylethyl	benzyl
2-methanesulfonylethyl	2-methoxyethyl
2-methanesulfonylethyl	2-hydroxyethyl
4-methanesulfonylaminobutyl	hydrogen
4-methanesulfonylaminobutyl	methyl
4-methanesulfonylaminobutyl	ethyl
4-methanesulfonylaminobutyl	n-propyl
4-methanesulfonylaminobutyl	n-butyl
4-methanesulfonylaminobutyl	benzyl
4-methanesulfonylaminobutyl	2-methoxyethyl
4-methanesulfonylaminobutyl	2-hydroxyethyl
2-(2-propanesulfonylamino)ethyl	hydrogen
2-(2-propanesulfonylamino)ethyl	methyl
2-(2-propanesulfonylamino)ethyl	ethyl
2-(2-propanesulfonylamino)ethyl	n-propyl
2-(2-propanesulfonylamino)ethyl	n-butyl
2-(2-propanesulfonylamino)ethyl	benzyl
2-(2-propanesulfonylamino)ethyl	2-methoxyethyl
2-(2-propanesulfonylamino)ethyl	2-hydroxyethyl
2-(benzenesulfonylamino)ethyl	hydrogen
2-(benzenesulfonylamino)ethyl	methyl
2-(benzenesulfonylamino)ethyl	ethyl
2-(benzenesulfonylamino)ethyl	n-propyl
2-(benzenesulfonylamino)ethyl	n-butyl
2-(benzenesulfonylamino)ethyl	benzyl

2-(benzenesulfonylamino)ethyl	2-methoxyethyl
2-(benzenesulfonylamino)ethyl	2-hydroxyethyl
2-(dimethylaminosulfonylamino)ethyl	hydrogen
2-(dimethylaminosulfonylamino)ethyl	methyl
2-(dimethylaminosulfonylamino)ethyl	ethyl
2-(dimethylaminosulfonylamino)ethyl	n-propyl
2-(dimethylaminosulfonylamino)ethyl	n-butyl
2-(dimethylaminosulfonylamino)ethyl	benzyl
2-(dimethylaminosulfonylamino)ethyl	2-methoxyethyl
2-(dimethylaminosulfonylamino)ethyl	2-hydroxyethyl
4-hydroxybutyl	hydrogen
4-hydroxybutyl	methyl
4-hydroxybutyl	ethyl
4-hydroxybutyl	n-propyl
4-hydroxybutyl	n-butyl
4-hydroxybutyl	benzyl
4-hydroxybutyl	2-methoxyethyl
4-hydroxybutyl	2-hydroxyethyl
2-aminoethyl	hydrogen
2-aminoethyl	methyl
2-aminoethyl	ethyl
2-aminoethyl	n-propyl
2-aminoethyl	n-butyl
2-aminoethyl	benzyl
2-aminoethyl	2-methoxyethyl
2-aminoethyl	2-hydroxyethyl
2-(cyclopropanecarbonylamino)ethyl	hydrogen
2-(cyclopropanecarbonylamino)ethyl	methyl
2-(cyclopropanecarbonylamino)ethyl	ethyl
2-(cyclopropanecarbonylamino)ethyl	n-propyl
2-(cyclopropanecarbonylamino)ethyl	n-butyl
2-(cyclopropanecarbonylamino)ethyl	benzyl
2-(cyclopropanecarbonylamino)ethyl	2-methoxyethyl
2-(cyclopropanecarbonylamino)ethyl	2-hydroxyethyl
2-(benzoylamino)ethyl	hydrogen
2-(benzoylamino)ethyl	methyl
2-(benzoylamino)ethyl	ethyl
2-(benzoylamino)ethyl	n-propyl
2-(benzoylamino)ethyl	n-butyl
2-(benzoylamino)ethyl	benzyl
2-(benzoylamino)ethyl	2-methoxyethyl
2-(benzoylamino)ethyl	2-hydroxyethyl
2-(benzoylamino)-2-methylpropyl	hydrogen
2-(benzoylamino)-2-methylpropyl	methyl
2-(benzoylamino)-2-methylpropyl	ethyl
2-(benzoylamino)-2-methylpropyl	n-propyl

2-(benzoylamino)-2-methylpropyl	n-butyl
2-(benzoylamino)-2-methylpropyl	benzyl
2-(benzoylamino)-2-methylpropyl	2-methoxyethyl
2-(benzoylamino)-2-methylpropyl	2-hydroxyethyl
2-(pyridine-3-carbonylamino)ethyl	hydrogen
2-(pyridine-3-carbonylamino)ethyl	methyl
2-(pyridine-3-carbonylamino)ethyl	ethyl
2-(pyridine-3-carbonylamino)ethyl	n-propyl
2-(pyridine-3-carbonylamino)ethyl	n-butyl
2-(pyridine-3-carbonylamino)ethyl	benzyl
2-(pyridine-3-carbonylamino)ethyl	2-methoxyethyl
2-(pyridine-3-carbonylamino)ethyl	2-hydroxyethyl
2-(2-propanecarbonylamino)ethyl	hydrogen
2-(2-propanecarbonylamino)ethyl	methyl
2-(2-propanecarbonylamino)ethyl	ethyl
2-(2-propanecarbonylamino)ethyl	n-propyl
2-(2-propanecarbonylamino)ethyl	n-butyl
2-(2-propanecarbonylamino)ethyl	benzyl
2-(2-propanecarbonylamino)ethyl	2-methoxyethyl
2-(2-propanecarbonylamino)ethyl	2-hydroxyethyl
4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyl	hydrogen
4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyl	methyl
4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyl	ethyl
4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyl	n-propyl
4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyl	n-butyl
4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyl	benzyl
4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyl	2-methoxyethyl
4-(1,3-dioxo-1,3-dihydroisoindol-2-yl)butyl	2-hydroxyethyl
2-(3-phenylureido)ethyl	hydrogen
2-(3-phenylureido)ethyl	methyl
2-(3-phenylureido)ethyl	ethyl
2-(3-phenylureido)ethyl	n-propyl
2-(3-phenylureido)ethyl	n-butyl
2-(3-phenylureido)ethyl	benzyl
2-(3-phenylureido)ethyl	2-methoxyethyl
2-(3-phenylureido)ethyl	2-hydroxyethyl
2-(3-pyridinylureido)ethyl	hydrogen
2-(3-pyridinylureido)ethyl	methyl
2-(3-pyridinylureido)ethyl	ethyl
2-(3-pyridinylureido)ethyl	n-propyl
2-(3-pyridinylureido)ethyl	n-butyl
2-(3-pyridinylureido)ethyl	benzyl
2-(3-pyridinylureido)ethyl	2-methoxyethyl
2-(3-pyridinylureido)ethyl	2-hydroxyethyl
2-[3,3-(dimethyl)ureido]ethyl	hydrogen
2-[3,3-(dimethyl)ureido]ethyl	methyl

2-[3,3-(dimethyl)ureido]ethyl	ethyl
2-[3,3-(dimethyl)ureido]ethyl	n-propyl
2-[3,3-(dimethyl)ureido]ethyl	n-butyl
2-[3,3-(dimethyl)ureido]ethyl	benzyl
2-[3,3-(dimethyl)ureido]ethyl	2-methoxyethyl
2-[3,3-(dimethyl)ureido]ethyl	2-hydroxyethyl

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IIIa, IIIb, IVa, VIa, VIIa, VIIIa, or IXa) and the following R_1, and R_2 substituents, wherein each line of the table represents a specific compound.

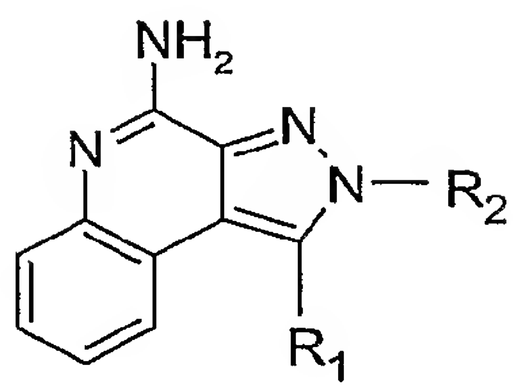


R_1	R_2
2-(propylsulfonyl)ethyl	hydrogen
2-(propylsulfonyl)ethyl	methyl
2-(propylsulfonyl)ethyl	ethyl
2-(propylsulfonyl)ethyl	n-propyl
2-(propylsulfonyl)ethyl	n-butyl
2-(propylsulfonyl)ethyl	benzyl
2-(propylsulfonyl)ethyl	2-methoxyethyl
2-(propylsulfonyl)ethyl	2-hydroxyethyl
2-hydroxy-2-methylpropyl	hydrogen
2-hydroxy-2-methylpropyl	methyl
2-hydroxy-2-methylpropyl	ethyl
2-hydroxy-2-methylpropyl	n-propyl
2-hydroxy-2-methylpropyl	n-butyl
2-hydroxy-2-methylpropyl	benzyl

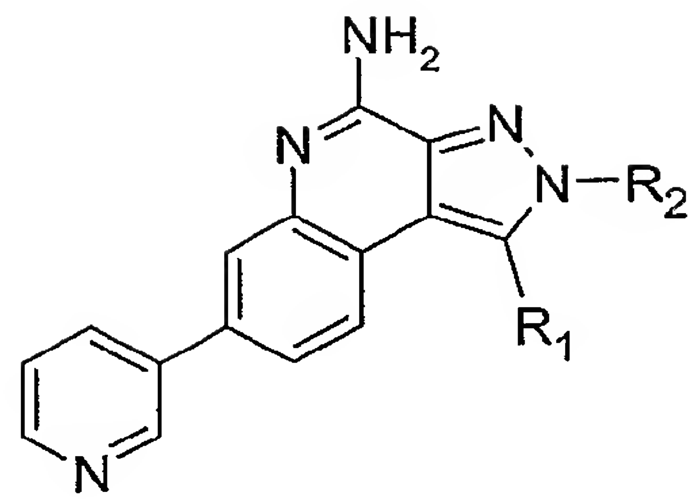
2-hydroxy-2-methylpropyl	2-methoxyethyl
2-hydroxy-2-methylpropyl	2-hydroxyethyl
2,2-dimethylpropyl	hydrogen
2,2-dimethylpropyl	methyl
2,2-dimethylpropyl	ethyl
2,2-dimethylpropyl	n-propyl
2,2-dimethylpropyl	n-butyl
2,2-dimethylpropyl	benzyl
2,2-dimethylpropyl	2-methoxyethyl
2,2-dimethylpropyl	2-hydroxyethyl
2-phenylethyl	hydrogen
2-phenylethyl	methyl
2-phenylethyl	ethyl
2-phenylethyl	n-propyl
2-phenylethyl	n-butyl
2-phenylethyl	benzyl
2-phenylethyl	2-methoxyethyl
2-phenylethyl	2-hydroxyethyl
2-[(cyclohexylcarbonyl)amino]-2-methylpropyl	hydrogen
2-[(cyclohexylcarbonyl)amino]-2-methylpropyl	methyl
2-[(cyclohexylcarbonyl)amino]-2-methylpropyl	ethyl
2-[(cyclohexylcarbonyl)amino]-2-methylpropyl	n-propyl
2-[(cyclohexylcarbonyl)amino]-2-methylpropyl	n-butyl
2-[(cyclohexylcarbonyl)amino]-2-methylpropyl	benzyl
2-[(cyclohexylcarbonyl)amino]-2-methylpropyl	2-methoxyethyl
2-[(cyclohexylcarbonyl)amino]-2-methylpropyl	2-hydroxyethyl
2-methyl-2-[(methylsulfonyl)amino]propyl	hydrogen
2-methyl-2-[(methylsulfonyl)amino]propyl	methyl
2-methyl-2-[(methylsulfonyl)amino]propyl	ethyl
2-methyl-2-[(methylsulfonyl)amino]propyl	n-propyl
2-methyl-2-[(methylsulfonyl)amino]propyl	n-butyl
2-methyl-2-[(methylsulfonyl)amino]propyl	benzyl
2-methyl-2-[(methylsulfonyl)amino]propyl	2-methoxyethyl
2-methyl-2-[(methylsulfonyl)amino]propyl	2-hydroxyethyl
2-(isobutyrylamino)-2-methylpropyl	hydrogen
2-(isobutyrylamino)-2-methylpropyl	methyl
2-(isobutyrylamino)-2-methylpropyl	ethyl
2-(isobutyrylamino)-2-methylpropyl	n-propyl
2-(isobutyrylamino)-2-methylpropyl	n-butyl
2-(isobutyrylamino)-2-methylpropyl	benzyl
2-(isobutyrylamino)-2-methylpropyl	2-methoxyethyl
2-(isobutyrylamino)-2-methylpropyl	2-hydroxyethyl
2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl	hydrogen
2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl	methyl
2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl	ethyl
2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl	n-propyl

2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl	n-butyl
2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl	benzyl
2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl	2-methoxyethyl
2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl	2-hydroxyethyl
2-{[(isopropylamino)carbonyl]amino}-2-methylpropyl	hydrogen
2-{[(isopropylamino)carbonyl]amino}-2-methylpropyl	methyl
2-{[(isopropylamino)carbonyl]amino}-2-methylpropyl	ethyl
2-{[(isopropylamino)carbonyl]amino}-2-methylpropyl	n-propyl
2-{[(isopropylamino)carbonyl]amino}-2-methylpropyl	n-butyl
2-{[(isopropylamino)carbonyl]amino}-2-methylpropyl	benzyl
2-{[(isopropylamino)carbonyl]amino}-2-methylpropyl	2-methoxyethyl
2-{[(isopropylamino)carbonyl]amino}-2-methylpropyl	2-hydroxyethyl
2-(acetylamino)-2-methylpropyl	hydrogen
2-(acetylamino)-2-methylpropyl	methyl
2-(acetylamino)-2-methylpropyl	ethyl
2-(acetylamino)-2-methylpropyl	n-propyl
2-(acetylamino)-2-methylpropyl	n-butyl
2-(acetylamino)-2-methylpropyl	benzyl
2-(acetylamino)-2-methylpropyl	2-methoxyethyl
2-(acetylamino)-2-methylpropyl	2-hydroxyethyl
4-(4-pyridin-2-ylpiperazin-1-yl)butyl	hydrogen
4-(4-pyridin-2-ylpiperazin-1-yl)butyl	methyl
4-(4-pyridin-2-ylpiperazin-1-yl)butyl	ethyl
4-(4-pyridin-2-ylpiperazin-1-yl)butyl	n-propyl
4-(4-pyridin-2-ylpiperazin-1-yl)butyl	n-butyl
4-(4-pyridin-2-ylpiperazin-1-yl)butyl	benzyl
4-(4-pyridin-2-ylpiperazin-1-yl)butyl	2-methoxyethyl
4-(4-pyridin-2-ylpiperazin-1-yl)butyl	2-hydroxyethyl
3-(3-pyridin-3-ylisoxazol-5-yl)propyl	hydrogen
3-(3-pyridin-3-ylisoxazol-5-yl)propyl	methyl
3-(3-pyridin-3-ylisoxazol-5-yl)propyl	ethyl
3-(3-pyridin-3-ylisoxazol-5-yl)propyl	n-propyl
3-(3-pyridin-3-ylisoxazol-5-yl)propyl	n-butyl
3-(3-pyridin-3-ylisoxazol-5-yl)propyl	benzyl
3-(3-pyridin-3-ylisoxazol-5-yl)propyl	2-methoxyethyl
3-(3-pyridin-3-ylisoxazol-5-yl)propyl	2-hydroxyethyl

Certain exemplary compounds, including some of those described above in the Examples, have the following Formula (IIIa, IIIb, IVa, VIa, VIIa, VIIIa, or IXa) and the following R_1, and R_2 substituents, wherein each line of the table represents a specific compound.



IIIa



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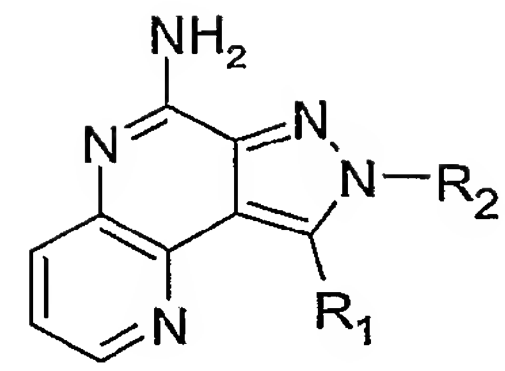
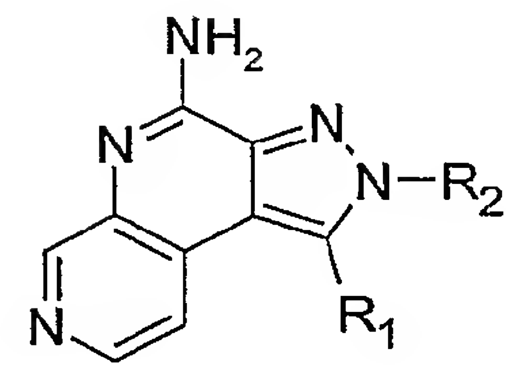
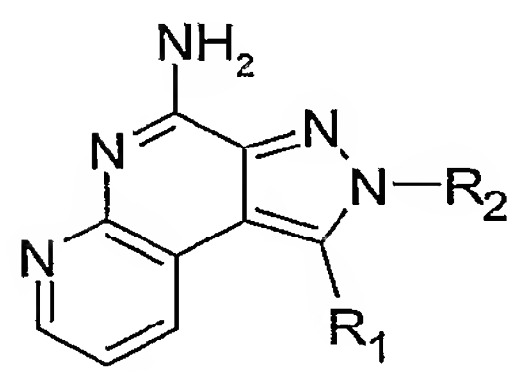


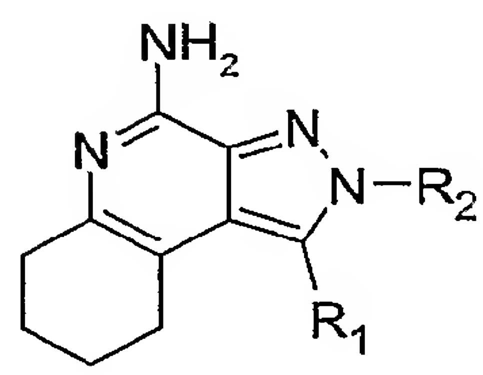
IVa



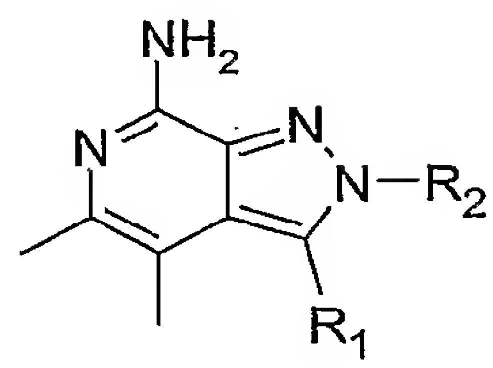
VIa



VIIa



VIIIa



IXa

R_1	R_2
n-butvl	hydrogen
n-butyl	methyl
n-butyl	ethyl
n-butyl	n-propyl
n-butyl	n-butyl
n-butyl	benzyl
n-butyl	2-methoxyethyl
n-butyl	2-hydroxyethyl
4-aminobutyl	hydrogen
4-aminobutyl	methyl
4-aminobutyl	ethyl
4-aminobutyl	n-propyl
4-aminobutyl	n-butyl
4-aminobutyl	benzyl
4-aminobutyl	2-methoxyethyl
4-aminobutyl	2-hydroxyethyl
2-amino-2-methylpropyl	hydrogen
2-amino-2-methylpropyl	methyl
2-amino-2-methylpropyl	ethyl
2-amino-2-methylpropyl	n-propyl
2-amino-2-methylpropyl	n-butyl
2-amino-2-methylpropyl	benzyl
2-amino-2-methylpropyl	2-methoxyethyl
2-amino-2-methylpropyl	2-hydroxyethyl
4-acetoxybutyl	hydrogen
4-acetoxybutyl	methyl
4-acetoxybutyl	ethyl

4-acetoxybutyl	n-propyl
4-acetoxybutyl	n-butyl
4-acetoxybutyl	benzyl
4-acetoxybutyl	2-methoxyethyl
4-acetoxybutyl	2-hydroxyethyl
4-(methylsulfonyl)butyl	hydrogen
4-(methylsulfonyl)butyl	methyl
4-(methylsulfonyl)butyl	ethyl
4-(methylsulfonyl)butyl	n-propyl
4-(methylsulfonyl)butyl	n-butyl
4-(methylsulfonyl)butyl	benzyl
4-(methylsulfonyl)butyl	2-methoxyethyl
4-(methylsulfonyl)butyl	2-hydroxyethyl
3-(phenylsulfonyl)propyl	hydrogen
3-(phenylsulfonyl)propyl	methyl
3-(phenylsulfonyl)propyl	ethyl
3-(phenylsulfonyl)propyl	n-propyl
3-(phenylsulfonyl)propyl	n-butyl
3-(phenylsulfonyl)propyl	benzyl
3-(phenylsulfonyl)propyl	2-methoxyethyl
3-(phenylsulfonyl)propyl	2-hydroxyethyl
2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl	hydrogen
2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl	methyl
2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl	ethyl
2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl	n-propyl
2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl	n-butyl
2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl	benzyl
2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl	2-methoxyethyl
2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl	2-hydroxyethyl
4-(aminosulfonyl)butyl	hydrogen
4-(aminosulfonyl)butyl	methyl
4-(aminosulfonyl)butyl	ethyl
4-(aminosulfonyl)butyl	n-propyl
4-(aminosulfonyl)butyl	n-butyl
4-(aminosulfonyl)butyl	benzyl
4-(aminosulfonyl)butyl	2-methoxyethyl
4-(aminosulfonyl)butyl	2-hydroxyethyl
4-[(methylamino)sulfonyl]butyl	hydrogen
4-[(methylamino)sulfonyl]butyl	methyl
4-[(methylamino)sulfonyl]butyl	ethyl
4-[(methylamino)sulfonyl]butyl	n-propyl
4-[(methylamino)sulfonyl]butyl	n-butyl
4-[(methylamino)sulfonyl]butyl	benzyl
4-[(methylamino)sulfonyl]butyl	2-methoxyethyl
4-[(methylamino)sulfonyl]butyl	2-hydroxyethyl
4-[(dimethylamino)sulfonyl]butyl	hydrogen

4-[(dimethylamino)sulfonyl]butyl	methyl
4-[(dimethylamino)sulfonyl]butyl	ethyl
4-[(dimethylamino)sulfonyl]butyl	n-propyl
4-[(dimethylamino)sulfonyl]butyl	n-butyl
4-[(dimethylamino)sulfonyl]butyl	benzyl
4-[(dimethylamino)sulfonyl]butyl	2-methoxyethyl
4-[(dimethylamino)sulfonyl]butyl	2-hydroxyethyl
2-[(cyclopropylcarbonyl)amino]-2-methylpropyl	hydrogen
2-[(cyclopropylcarbonyl)amino]-2-methylpropyl	methyl
2-[(cyclopropylcarbonyl)amino]-2-methylpropyl	ethyl
2-[(cyclopropylcarbonyl)amino]-2-methylpropyl	n-propyl
2-[(cyclopropylcarbonyl)amino]-2-methylpropyl	n-butyl
2-[(cyclopropylcarbonyl)amino]-2-methylpropyl	benzyl
2-[(cyclopropylcarbonyl)amino]-2-methylpropyl	2-methoxyethyl
2-[(cyclopropylcarbonyl)amino]-2-methylpropyl	2-hydroxyethyl
2-methyl-2-(propionylamino)propyl	hydrogen
2-methyl-2-(propionylamino)propyl	methyl
2-methyl-2-(propionylamino)propyl	ethyl
2-methyl-2-(propionylamino)propyl	n-propyl
2-methyl-2-(propionylamino)propyl	n-butyl
2-methyl-2-(propionylamino)propyl	benzyl
2-methyl-2-(propionylamino)propyl	2-methoxyethyl
2-methyl-2-(propionylamino)propyl	2-hydroxyethyl
2-[(4-fluorobenzoyl)amino]-2-methylpropyl	hydrogen
2-[(4-fluorobenzoyl)amino]-2-methylpropyl	methyl
2-[(4-fluorobenzoyl)amino]-2-methylpropyl	ethyl
2-[(4-fluorobenzoyl)amino]-2-methylpropyl	n-propyl
2-[(4-fluorobenzoyl)amino]-2-methylpropyl	n-butyl
2-[(4-fluorobenzoyl)amino]-2-methylpropyl	benzyl
2-[(4-fluorobenzoyl)amino]-2-methylpropyl	2-methoxyethyl
2-[(4-fluorobenzoyl)amino]-2-methylpropyl	2-hydroxyethyl
2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl	hydrogen
2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl	methyl
2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl	ethyl
2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl	n-propyl
2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl	n-butyl
2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl	benzyl
2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl	2-methoxyethyl
2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl	2-hydroxyethyl
2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl	hydrogen
2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl	methyl
2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl	ethyl
2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl	n-propyl
2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl	n-butyl
2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl	benzyl
2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl	2-methoxyethyl

2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl	2-hydroxyethyl
3-(3-methylisoxazol-5-yl)propyl	hydrogen
3-(3-methylisoxazol-5-yl)propyl	methyl
3-(3-methylisoxazol-5-yl)propyl	ethyl
3-(3-methylisoxazol-5-yl)propyl	n-propyl
3-(3-methylisoxazol-5-yl)propyl	n-butyl
3-(3-methylisoxazol-5-yl)propyl	benzyl
3-(3-methylisoxazol-5-yl)propyl	2-methoxyethyl
3-(3-methylisoxazol-5-yl)propyl	2-hydroxyethyl
3-(3-isopropyllisoxazol-5-yl)propyl	hydrogen
3-(3-isopropyllisoxazol-5-yl)propyl	methyl
3-(3-isopropyllisoxazol-5-yl)propyl	ethyl
3-(3-isopropyllisoxazol-5-yl)propyl	n-propyl
3-(3-isopropyllisoxazol-5-yl)propyl	n-butyl
3-(3-isopropyllisoxazol-5-yl)propyl	benzyl
3-(3-isopropyllisoxazol-5-yl)propyl	2-methoxyethyl
3-(3-isopropyllisoxazol-5-yl)propyl	2-hydroxyethyl
3-(3-phenylisoxazol-5-yl)propyl	hydrogen
3-(3-phenylisoxazol-5-yl)propyl	methyl
3-(3-phenylisoxazol-5-yl)propyl	ethyl
3-(3-phenylisoxazol-5-yl)propyl	n-propyl
3-(3-phenylisoxazol-5-yl)propyl	n-butyl
3-(3-phenylisoxazol-5-yl)propyl	benzyl
3-(3-phenylisoxazol-5-yl)propyl	2-methoxyethyl
3-(3-phenylisoxazol-5-yl)propyl	2-hydroxyethyl
4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5H)-yl)butyl	hydrogen
4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5H)-yl)butyl	methyl
4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5H)-yl)butyl	ethyl
4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5H)-yl)butyl	n-propyl
4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5H)-yl)butyl	n-butyl
4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5H)-yl)butyl	benzyl
4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5H)-yl)butyl	2-methoxyethyl
4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5H)-yl)butyl	2-hydroxyethyl
4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl	hydrogen
4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl	methyl
4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl	ethyl
4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl	n-propyl
4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl	n-butyl
4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl	benzyl
4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl	2-methoxyethyl
4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl	2-hydroxyethyl
pent-4-ynyl	hydrogen
pent-4-ynyl	methyl
pent-4-ynyl	ethyl
pent-4-ynyl	n-propyl
pent-4-ynyl	n-butyl

pent-4-ynyl	benzyl
pent-4-ynyl	2-methoxyethyl
pent-4-ynyl	2-hydroxyethyl

Compounds of the invention have been found to modulate cytokine biosynthesis by inducing the production of interferon α and/or tumor necrosis factor α when tested using the method described below.

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4×10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF-α) when tested using the method described below.

TNF-α INHIBITION IN MOUSE CELLS

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor-α (TNF-α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3×10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100 μL) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3×10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5μM. LPS (Lipopolysaccaride from *Salmonella typhimurium,* Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by a dose response assay.

Incubation

A solution of test compound (1μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource

International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4 x 10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 μL) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1 x 10^5 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by dose response assay.

Incubation

A solution of test compound (200 μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

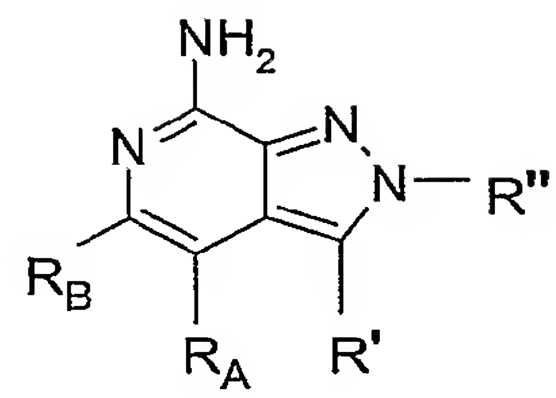
TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. The present invention has been described with reference to several embodiments thereof. The foregoing illustrative embodiments and examples have been provided for clarity of understanding only, and no unnecessary limitations are to be understood therefrom. It will be apparent to those skilled in the art that many changes can be made to the described embodiments without departing from the spirit and scope of the invention. Thus, the scope of the invention is intended to be limited only by the claims that follow.

WHAT IS CLAIMED IS:

1. A compound of the formula (I):



I

wherein:

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R' and R" are independently selected from the group consisting of hydrogen and non-interfering substitutents;

R"' is a non-interfering substitutent; and

R_9 is selected from the group consisting of hydrogen and alkyl;

with the proviso that at least one of R_A, R_B, R', or R" is other than hydrogen; and with the further proviso that when R_A and R_B form a benzene ring unsubstituted or substituted with chloro, and R' is hydrogen, then R" is other than phenyl or phenyl substituted with methyl, methoxy, chloro, or fluoro;

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio and

$-N(R_9)_2$;

3. The compound or salt of claim 1 wherein R_A and R_B form a fused aryl or heteroaryl ring.

4. The compound or salt of claim 1 wherein R_A and R_B form a fused 5 to 7 membered saturated ring.

5. The compound or salt of any one of claims 1 through 4 wherein R' is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

-X-Y-X-Y-R_4, and

-X-R_5; wherein

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

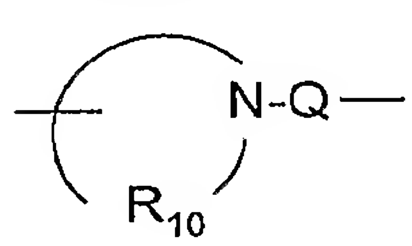
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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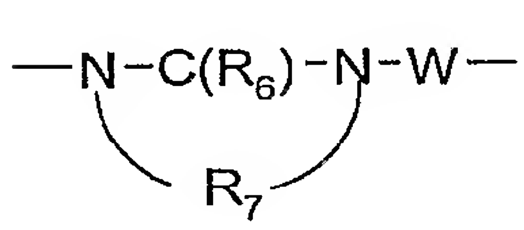

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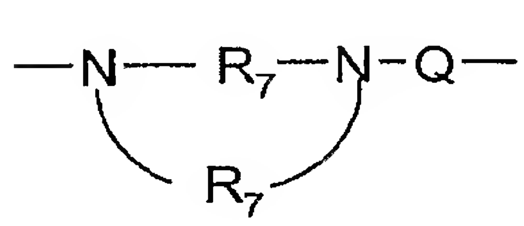

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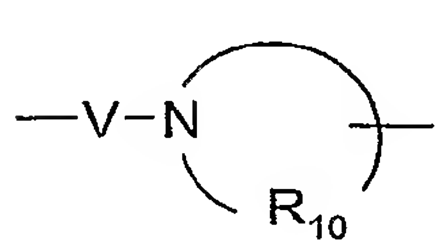

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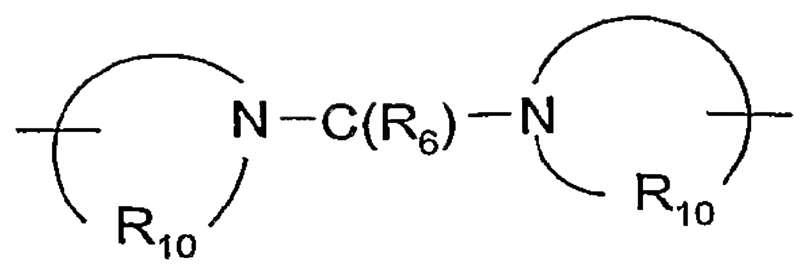
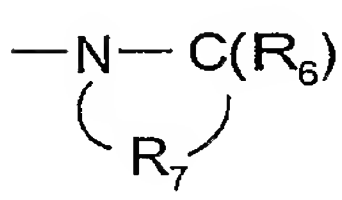
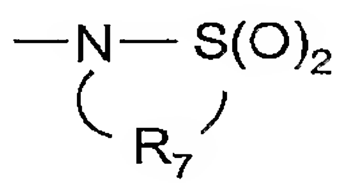
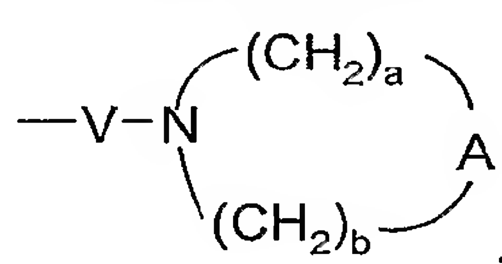
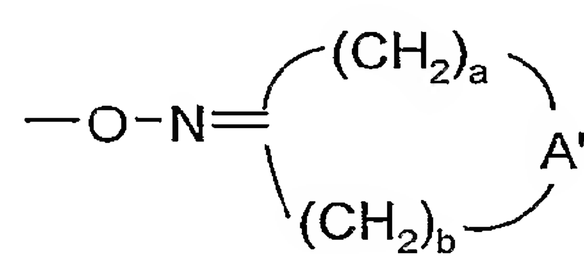
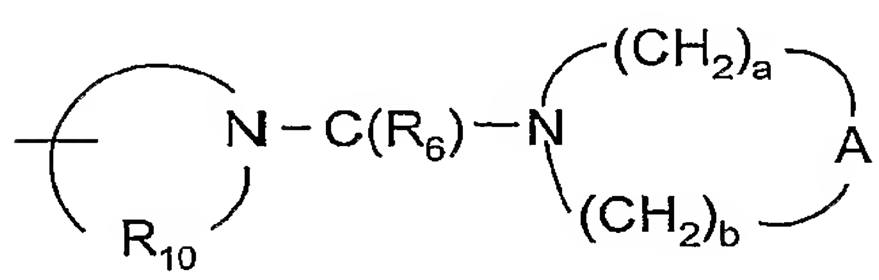

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

 ,  ,  ,  , and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$,

$-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7.

6. The compound or salt of any one of claims 1 through 4 wherein R' is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X^1-Y^1-R_4$, and

$-X-R_5$; wherein

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group;

Y is selected from the group consisting of:

-O-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

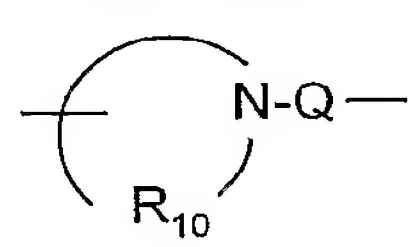
-C(O)-,

-C(O)-O-,

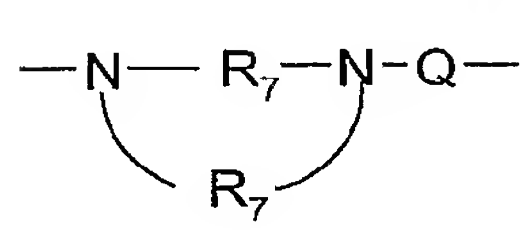
-O-C(O)-,

$-N(R_8)-Q-$,

$-C(O)-N(R_8)-$,



, and



;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of:

-S-,

-C(O)-,

-C(O)-O-,

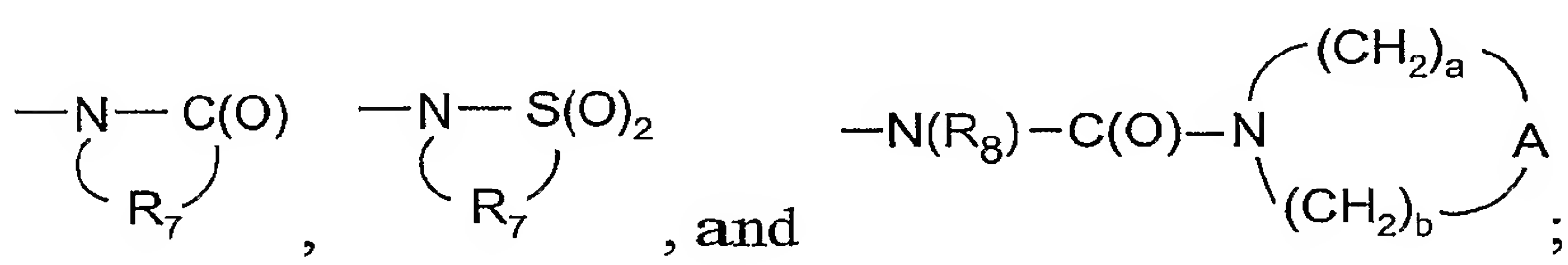
-C(O)-N(R_8)-,

-S(O)$_2$-N(R_8)-, and

-N(R_8)-C(O)-;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, and –N(R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7.

7. The compound or salt of any one of claims 1 through 6 wherein R" is selected from the group consisting of

-R_4,

-X-R_4,

-X-Y-R_4, and

-X-R_5; wherein

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

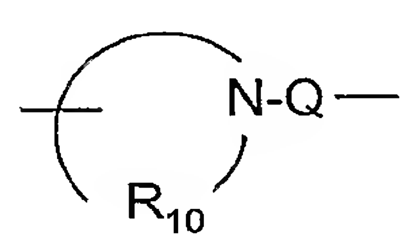
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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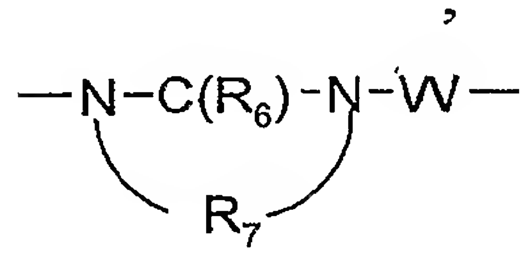

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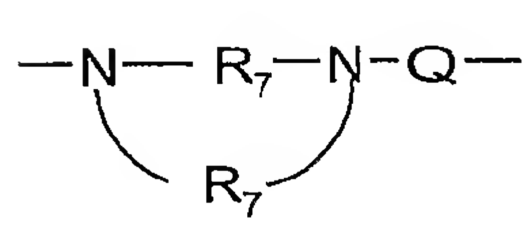

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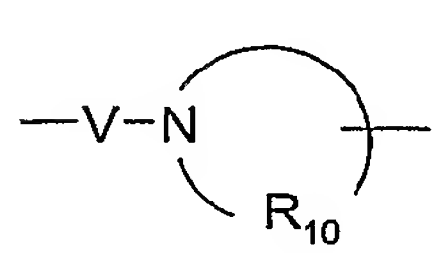

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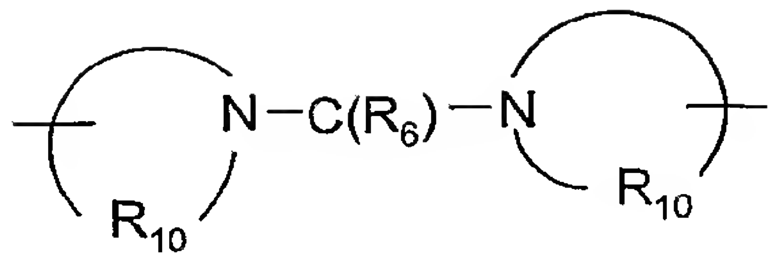
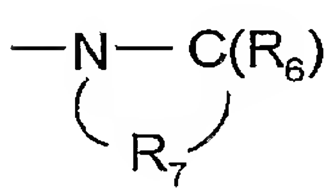
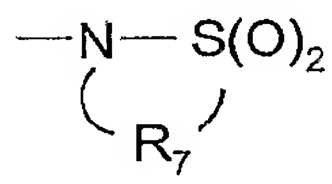
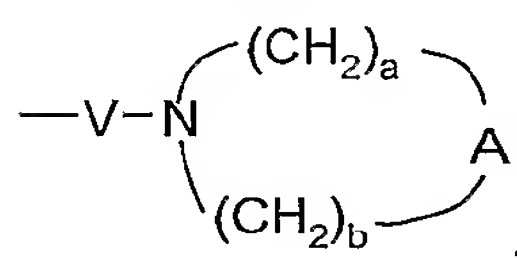
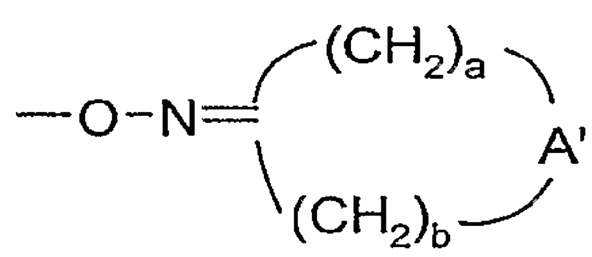
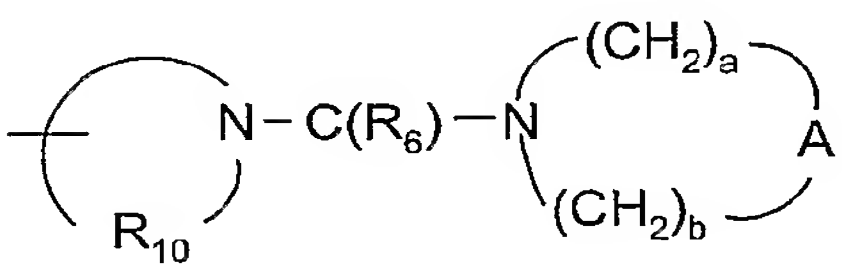

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of


, 
, 
, 
, and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and

-$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

8. The compound or salt of claim 7 wherein R" is selected from the group consisting of:

-R_4,

-X-R_4, and

-X-Y-R_4; wherein

X is alkylene that is optionally terminated by arylene or heterocyclylene;

Y is selected from the group consisting of:

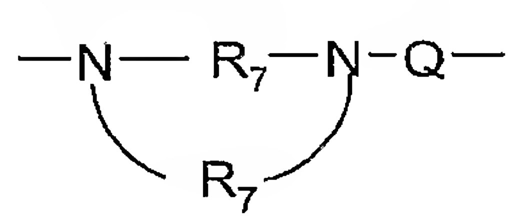
-$S(O)_2$-,

-C(O)-,

-C(O)-O-,

-N(R_8)-Q-,

-C(O)-N(R_8)-, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, heterocyclyl, and heteroaryl, wherein the alkyl, aryl, aryloxyalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, and in the case of heterocyclyl, oxo;

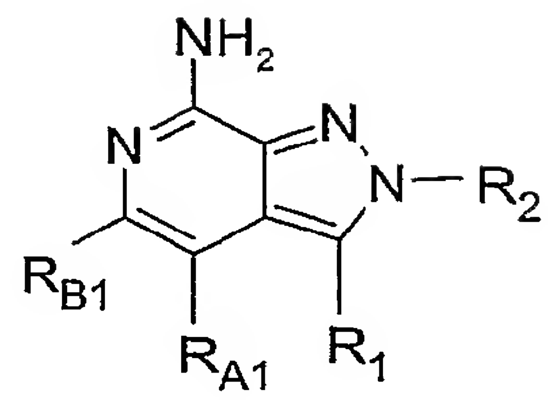
R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is in selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl; and

Q is selected from the group consisting of a bond, -C(O)-, -$S(O)_2$-, -C(R_6)-N(R_8)-, and -$S(O)_2$-N(R_8)-.

9. A compound of the formula (II):



II

wherein:

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio and

$-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

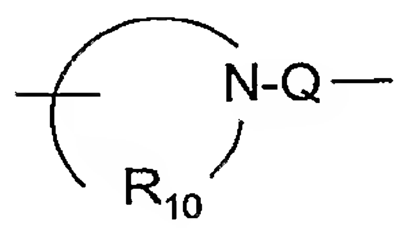
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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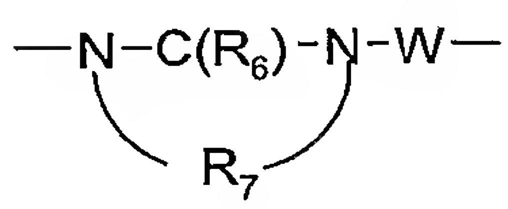

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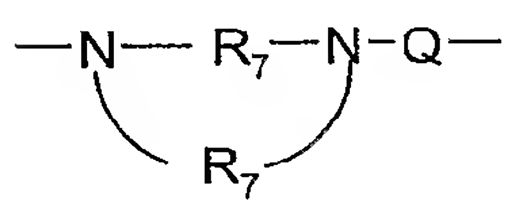

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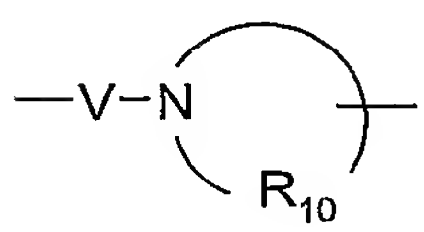

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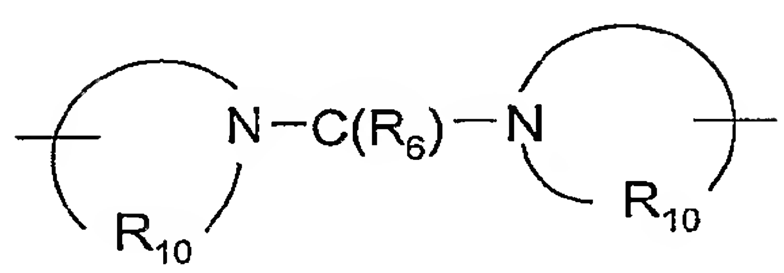
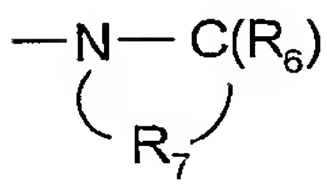
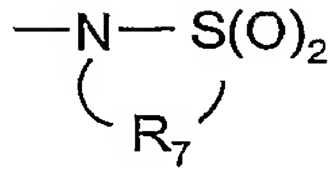
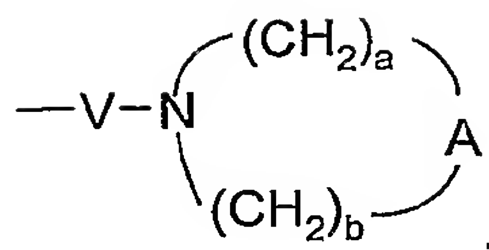
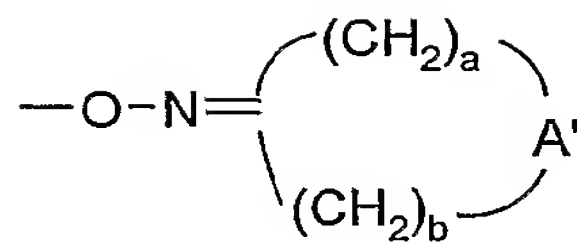


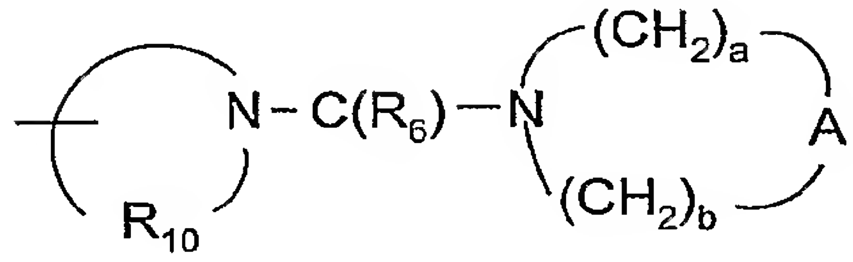
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, and -$N(R_4)$-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -$S(O)_2$-, -C(R_6)-N(R_8)-W-, -$S(O)_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and -$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

with the proviso that at least one of R_{A1}, R_{B1}, R_1, or R_2 is other than hydrogen; and with the further proviso that when R_{A1} and R_{B1} form a fused benzene ring unsubstituted or substituted with chloro, and R_1 is hydrogen, then R_2 is other than phenyl or phenyl substituted with methyl, methoxy, chloro, or fluoro;

or a pharmaceutically acceptable salt thereof.

10. The compound or salt of claim 9 wherein R_{A1} and R_{B1} form a fused benzene ring which is unsubstituted.

11. The compound or salt of claim 9 wherein R_{A1} and R_{B1} form a fused pyridine ring which is unsubstituted.

12. The compound or salt of claim 9 wherein R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted.

13. The compound or salt of any one of claims 9 through 12 wherein R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X^1-Y^1-R_4$, and

$-X-R_5$; wherein

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group;

Y is selected from the group consisting of:

-O-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

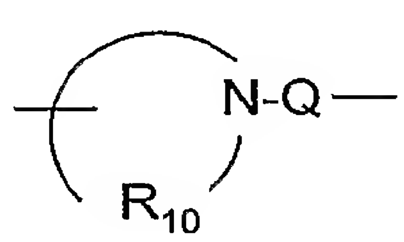
-C(O)-,

-C(O)-O-,

-O-C(O)-,

$-N(R_8)-Q-$,

$-C(O)-N(R_8)-$,



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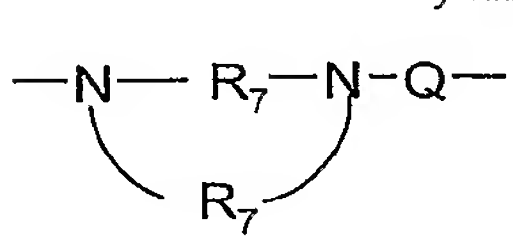


;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of:

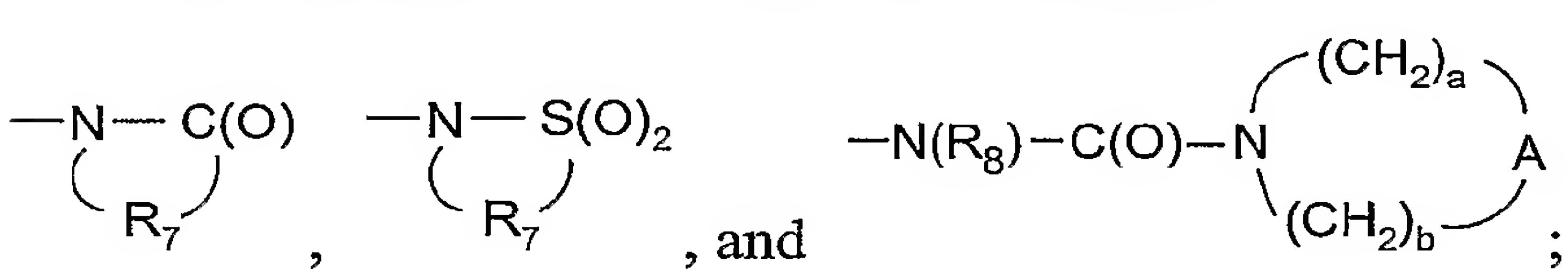
-S-,

-C(O)-,

-C(O)-O-,
-C(O)-N(R_8)-,
-S(O)$_2$-N(R_8)-, and
-N(R_8)-C(O)-;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, and –N(R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7.

14. The compound or salt of claim 13 wherein R_1 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkynyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl, aryl-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl-O-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-4} alkyl-C(O)-O-C_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl,

aryl-C(O)-NH-C_{1-4} alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-$S(O)_2$-NH-C_{1-4} alkylenyl, aryl-$S(O)_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-$S(O)_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-$S(O)_2$-C_{1-4} alkylenyl, amino-$S(O)_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one or two substituents selected from the group consisting of heteroaryl and oxo.

15. The compound or salt of any one of claims 9 through 14 wherein R_2 is selected from the group consisting of:

-R_4,

-X-R_4, and

-X-Y-R_4; wherein

X is alkylene that is optionally terminated by arylene or heterocyclylene;

Y is selected from the group consisting of:

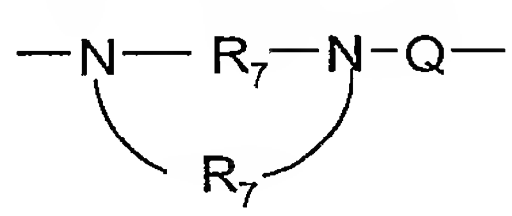
-$S(O)_2$-,

-C(O)-,

-C(O)-O-,

-N(R_8)-Q-,

-C(O)-N(R_8)-, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, heterocyclyl, and heteroaryl, wherein the alkyl, aryl, aryloxyalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, and in the case of heterocyclyl, oxo;

R_6 is selected from the group consisting of =O and =S;

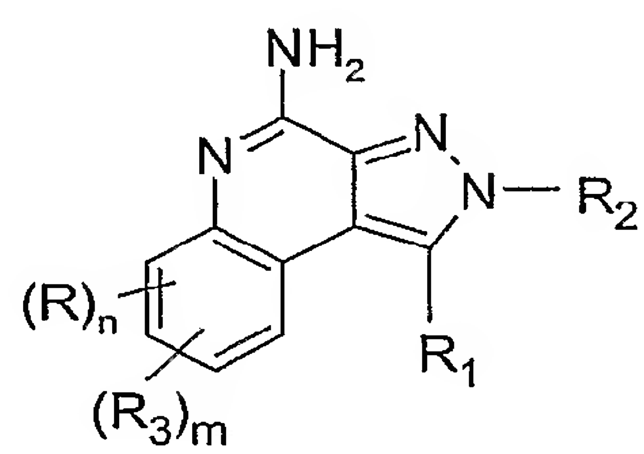
R_7 is C_{2-7} alkylene;

R_8 is in selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl; and

Q is selected from the group consisting of a bond, -C(O)-, -S(O)$_2$-, -C(R_6)-N(R_8)-, and -S(O)$_2$-N(R_8)-.

16. The compound or salt of claim 15 wherein R_2 is selected from the group consisting of hydrogen, C_{1-5} alkyl, C_{1-4} alkoxyC_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, and arylC_{1-4} alkylenyl wherein aryl is unsubstituted or substituted by one or more substituents selected from the group consisting of chloro, fluoro, methoxy, methyl, cyano, and methoxycarbonyl.

17. A compound of the formula (III):



III

wherein:

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

$-Z-X-Y-X-Y-R_4$, and

$-Z-X-R_5$;

n is 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

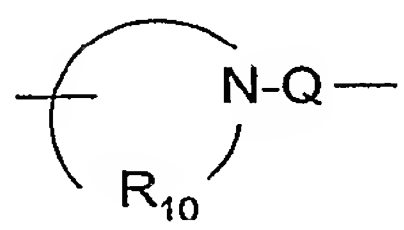
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

$-CH(-N(-O-R_8)-Q-R_4)-$,



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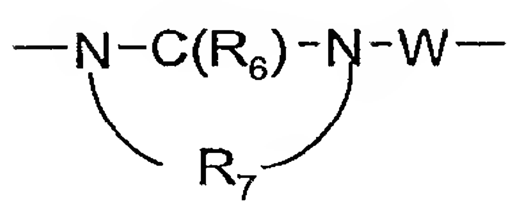

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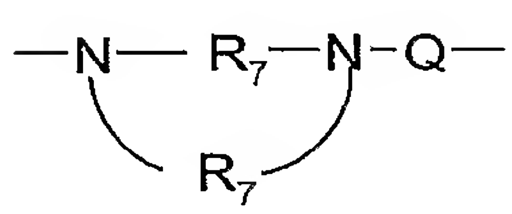

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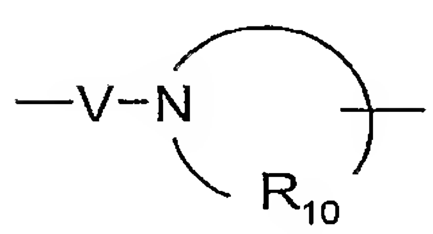

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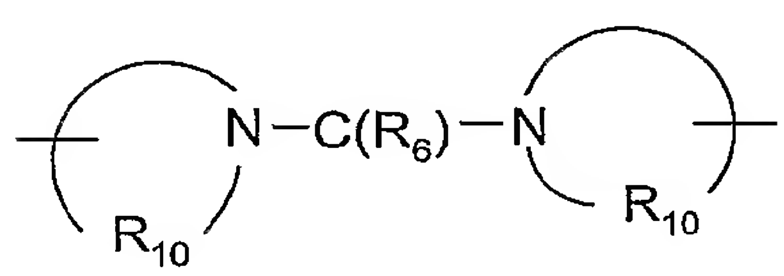
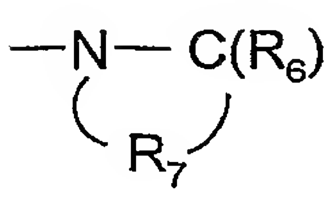
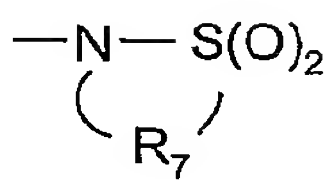
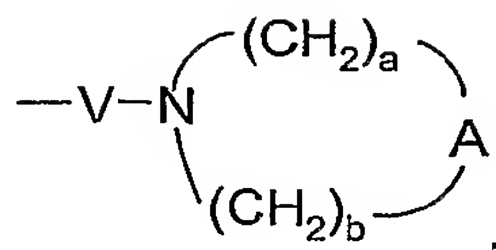
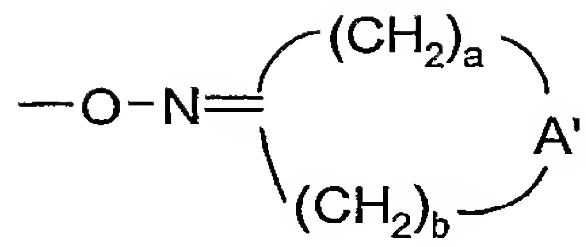


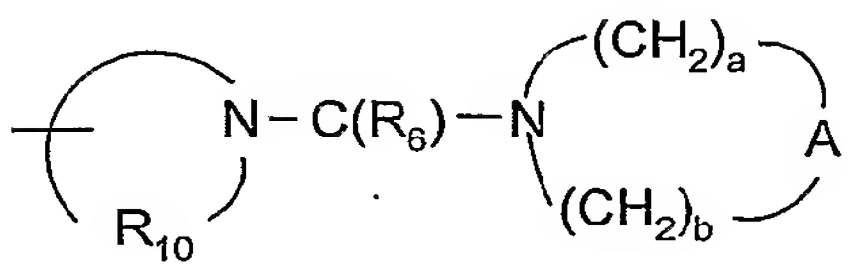
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

with the proviso that when R_1 is hydrogen, m is 0, and R is chloro, then R_2 is other than phenyl or phenyl substituted with methyl, methoxy, chloro, or fluoro;

or a pharmaceutically acceptable salt thereof.

18. The compound or salt of claim 17 wherein R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X^1-Y^1-R_4$, and

$-X-R_5$; wherein

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group;

Y is selected from the group consisting of:

-O-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

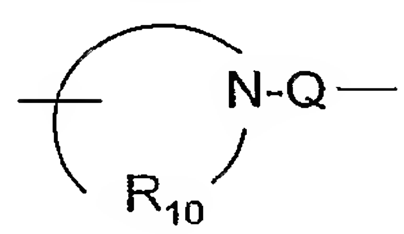
-C(O)-,

-C(O)-O-,

-O-C(O)-,

$-N(R_8)-Q-$,

$-C(O)-N(R_8)-$,



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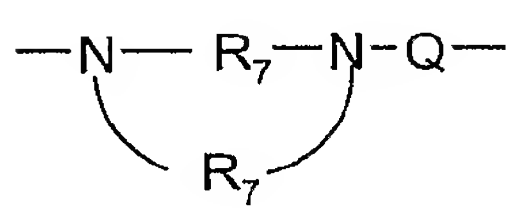


;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of:

-S-,

-C(O)-,

-C(O)-O-,

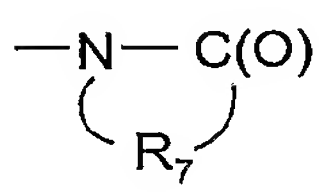
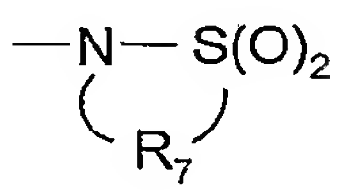
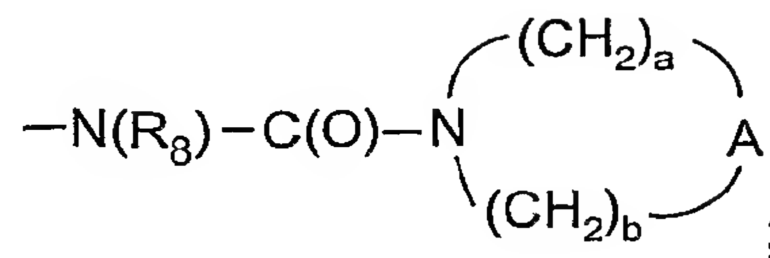
$-C(O)-N(R_8)-$,

$-S(O)_2-N(R_8)-$, and

$-N(R_8)-C(O)-$;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

 ,  , and  ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, and –N(R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7.

19. The compound or salt of claim 18 wherein R_1 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkynyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl, aryl-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl-O-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-4} alkyl-C(O)-O-C_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl, aryl-C(O)-NH-C_{1-4} alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-S(O)$_2$-C_{1-4} alkylenyl, amino-S(O)$_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one or two substituents selected from the group consisting of heteroaryl and oxo.

20. The compound or salt of claim 19 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, butyl, pent-4-ynyl, 2-phenylethyl, 2-hydroxy-2-methylpropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-methanesulfonylethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 4-methanesulfonylaminobutyl, 2-methyl-2-[(methylsulfonyl)aminopropyl, 2-(2-propanesulfonylamino)ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-(isobutyrylamino)-2-methylpropyl, 2-methyl-2-(propionylamino)propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-(isobutyrylamino)ethyl, 2-{[(isopropylamino)carbonyl]amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

21. The compound or salt of any one of claims 17 through 20 wherein R_2 is selected from the group consisting of:

$-R_4$,

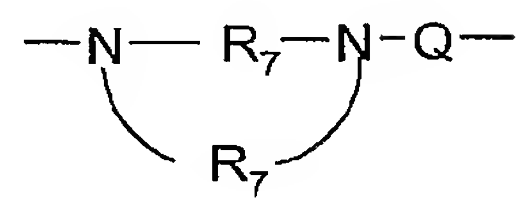
$-X-R_4$, and

$-X-Y-R_4$; wherein

X is alkylene that is optionally terminated by arylene or heterocyclylene;

Y is selected from the group consisting of:

-$S(O)_2$-,
-C(O)-,
-C(O)-O-,
-$N(R_8)$-Q-,
-C(O)-$N(R_8)$-, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, heterocyclyl, and heteroaryl, wherein the alkyl, aryl, aryloxyalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, and in the case of heterocyclyl, oxo;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is in selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl; and

Q is selected from the group consisting of a bond, -C(O)-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-, and -$S(O)_2$-$N(R_8)$-.

22. The compound or salt of any one of claims 17 through 21 wherein R_2 is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl, and hydroxyalkylenyl.

23. The compound or salt of any one of claims 17 through 21 wherein R_2 is selected from the group consisting of hydrogen, C_{1-5} alkyl, C_{1-4} alkoxyC_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, and arylC_{1-4} alkylenyl wherein aryl is unsubstituted or substituted by one or more substituents selected from the group consisting of chloro, fluoro, methoxy, methyl, cyano, and methoxycarbonyl.

24. The compound or salt of claim 17 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl; and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, and benzyl.

25. The compound or salt of any one of claims 17 through 24 wherein R is selected from the group consisting of hydroxy and methoxy, m is 0, and n is 1.

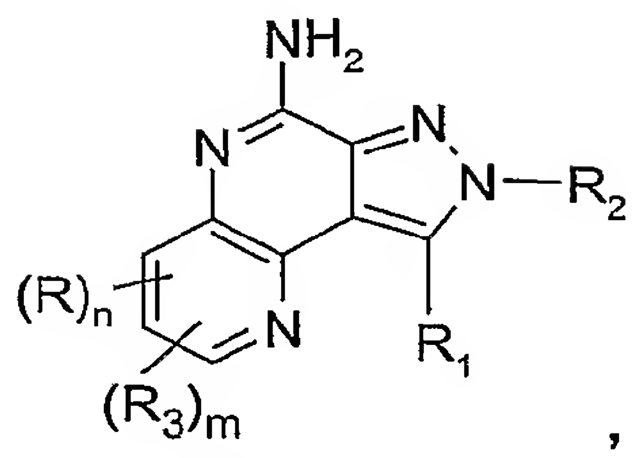
26. The compound or salt of any one of claims 17 through 24 wherein R_3 is selected from the group consisting of aryl, arylalkyleneoxy, and heteroaryl, wherein aryl, arylalkyleneoxy, and heteroaryl are unsubstituted or substituted with one or more substituents selected from the group consisting of alkyl and halogen, m is 1, and n is 0.

27. The compound or salt of claim 26 wherein R_3 is selected from the group consisting of phenyl, benzyloxy, 3-furyl, pyridin-3-yl, *p*-toluyl, (4-chlorobenzyl)oxy, and (4-methylbenzyl)oxy.

28. The compound or salt of any one of claims 17 through 24 wherein n is 0, or m is 0.

29. The compound or salt of any one of claims 17 through 24 wherein m and n are 0.

30. A compound selected from the group consisting of the formulas (IV, V, VI, and VII):


IV
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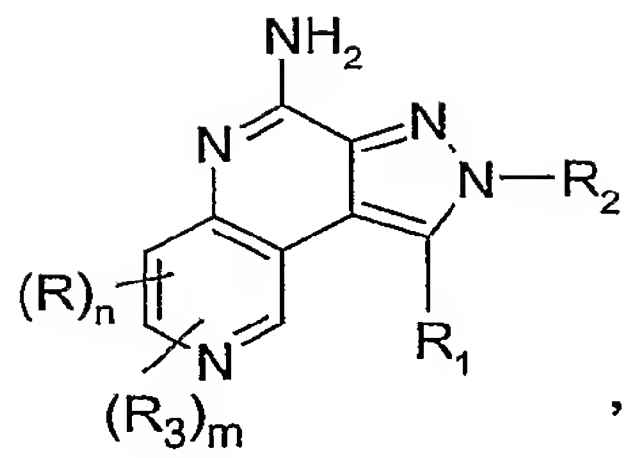
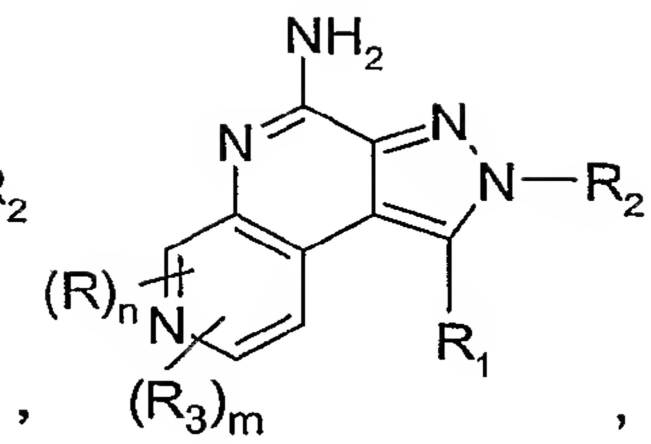
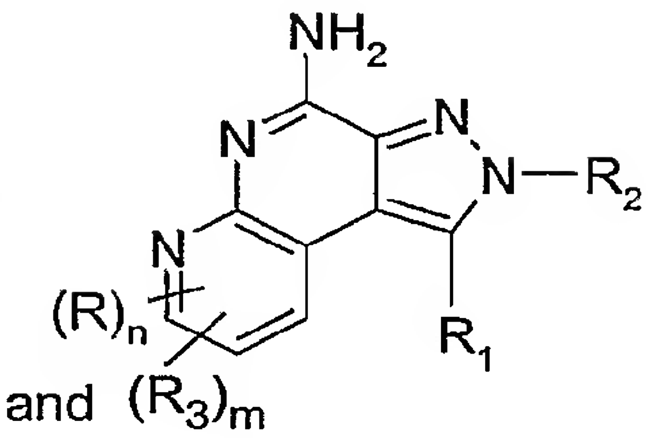

V
,

VI
, and

VII

wherein:

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X-R_4$,

$-Z-X-Y-R_4$,

-Z-X-Y-X-Y-R_4, and

-Z-X-R_5;

n is 0 or 1;

m is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

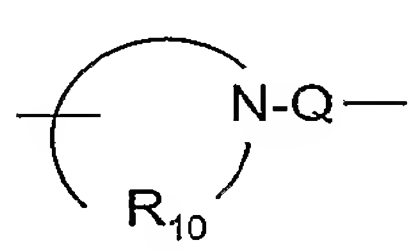
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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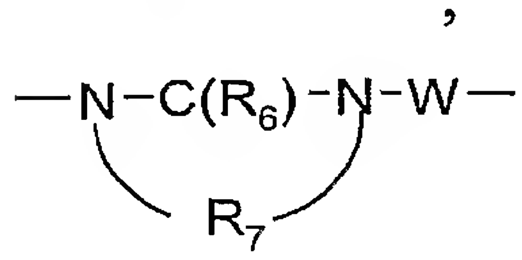

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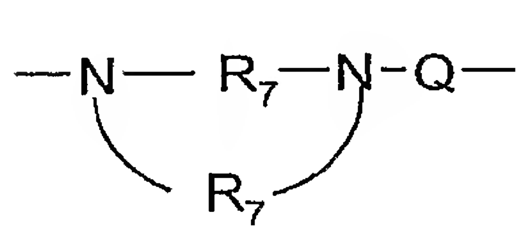

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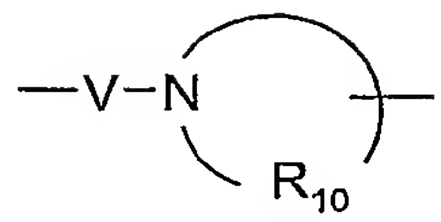

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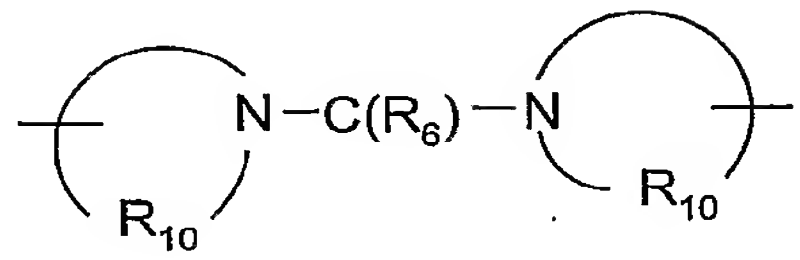
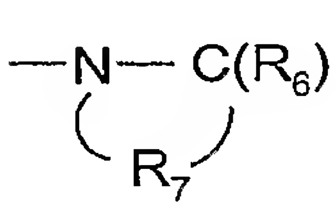
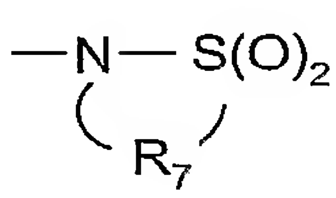
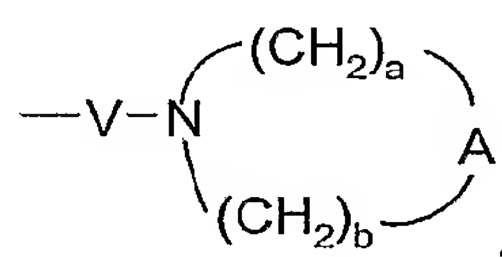
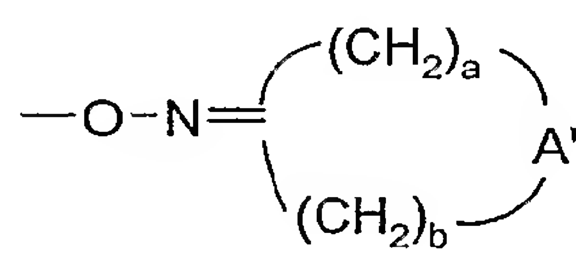


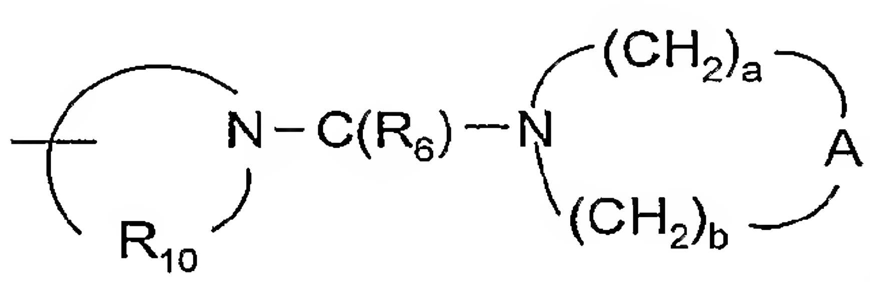
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

 ,  ,  ,  , and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

31. The compound or salt of claim 30 wherein n is 0, or m is 0.

32. The compound or salt of claim 30 wherein n and m are 0.

33. The compound or salt of any one of claims 30 through 32 wherein R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X^1-Y^1-R_4$, and

$-X-R_5$; wherein

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group;

Y is selected from the group consisting of:

-O-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

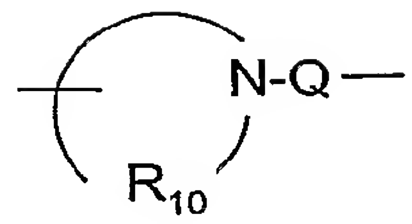
-C(O)-,

-C(O)-O-,

-O-C(O)-,

$-N(R_8)-Q-$,

$-C(O)-N(R_8)-$,



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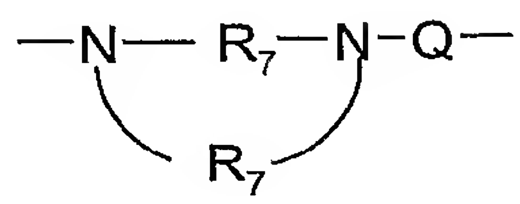


;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of:

-S-,

-C(O)-,

-C(O)-O-,

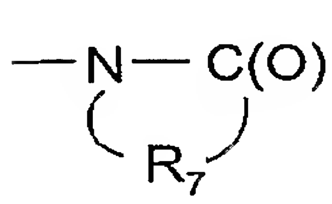
-C(O)-N(R_8)-,

-S(O)$_2$-N(R_8)-, and

-N(R_8)-C(O)-;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



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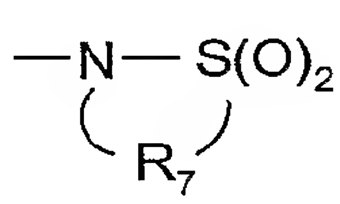

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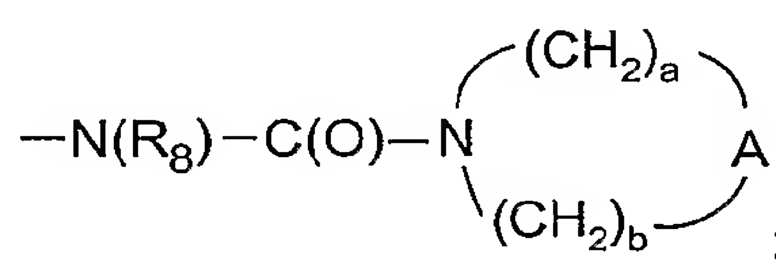


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, and –N(R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

34. The compound or salt of claim 33 wherein R_1 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkynyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-$S(O)_2$-C_{1-4} alkylenyl, aryl-$S(O)_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-$S(O)_2$-C_{1-4} alkylenyl-O-C_{1-4} alkylenyl, C_{1-4} alkyl-$S(O)_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-4} alkyl-C(O)-O-C_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl, aryl-C(O)-NH-C_{1-4} alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-$S(O)_2$-NH-C_{1-4} alkylenyl, aryl-$S(O)_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-$S(O)_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-$S(O)_2$-C_{1-4} alkylenyl, amino-$S(O)_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one or two substituents selected from the group consisting of heteroaryl and oxo.

35. The compound or salt of claim 34 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, butyl, pent-4-ynyl, 2-phenylethyl, 2-hydroxy-2-methylpropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-methanesulfonylethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 4-methanesulfonylaminobutyl, 2-methyl-2-[(methylsulfonyl)aminopropyl, 2-(2-propanesulfonylamino)ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-(isobutyrylamino)-2-methylpropyl, 2-methyl-2-(propionylamino)propyl,

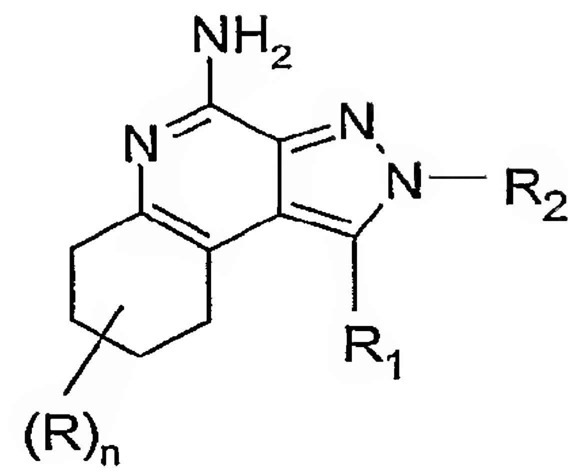
2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-(isobutyrylamino)ethyl, 2-{[(isopropylamino)carbonyl]amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

36. The compound or salt of any one of claims 30 through 35 wherein R_2 is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl, and hydroxyalkylenyl.

37. The compound or salt of any one of claims 30 through 35 wherein R_2 is selected from the group consisting of hydrogen, C_{1-5} alkyl, C_{1-4} alkoxyC_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, and arylC_{1-4} alkylenyl wherein aryl is unsubstituted or substituted by one or more substituents selected from the group consisting of chloro, fluoro, methoxy, methyl, cyano, and methoxycarbonyl.

38. The compound or salt of claim 32 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl; and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, and benzyl.

39. A compound of the formula (VIII):



VIII

wherein:

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$;

n is 0 to 4;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

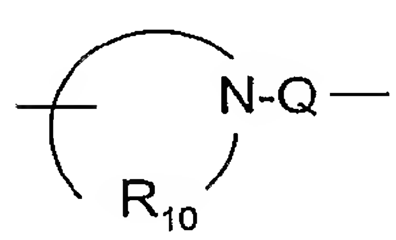
$-C(R_6)-N(OR_9)-$,

$-O-N(R_8)-Q-$,

$-O-N=C(R_4)-$,

$-C(=N-O-R_8)-$,

$-CH(-N(-O-R_8)-Q-R_4)-$,



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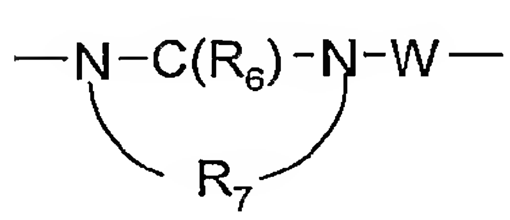

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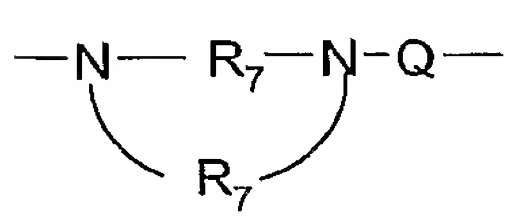

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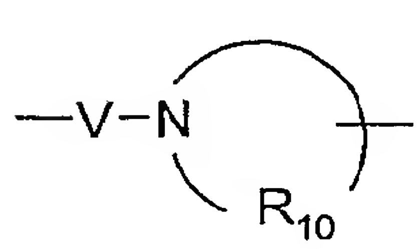

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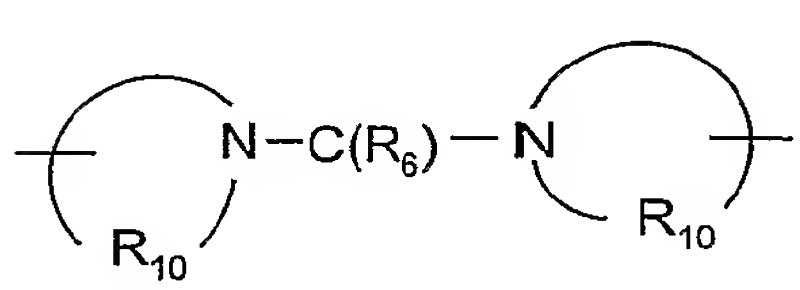
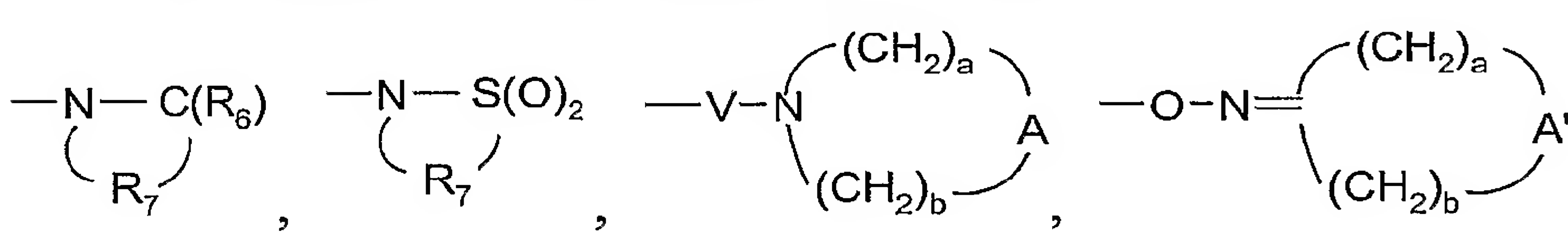


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



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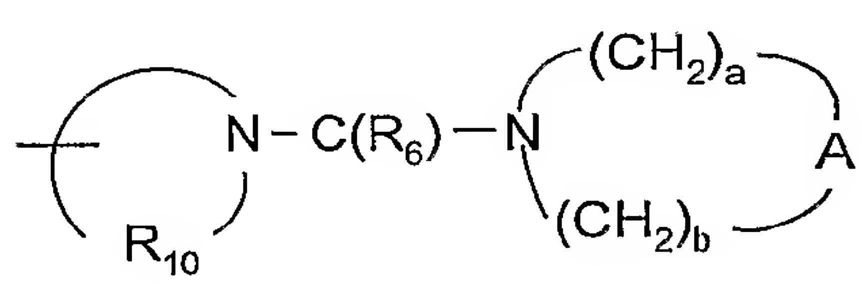


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, and –N(R_4)-;

A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH$_2$-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

40. The compound or salt of claim 39 wherein n is 0.

41. The compound or salt of claim 39 or 40 wherein R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X^1-Y^1-R_4$, and

$-X-R_5$; wherein

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted by one -O- group;

Y is selected from the group consisting of:

-O-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

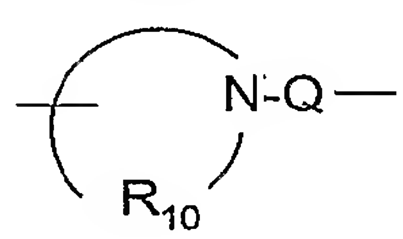
-C(O)-,

-C(O)-O-,

-O-C(O)-,

$-N(R_8)-Q-$,

$-C(O)-N(R_8)-$,



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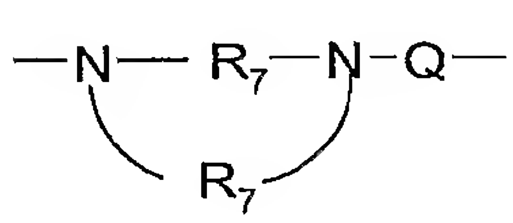


;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of:

-S-,

-C(O)-,

-C(O)-O-,

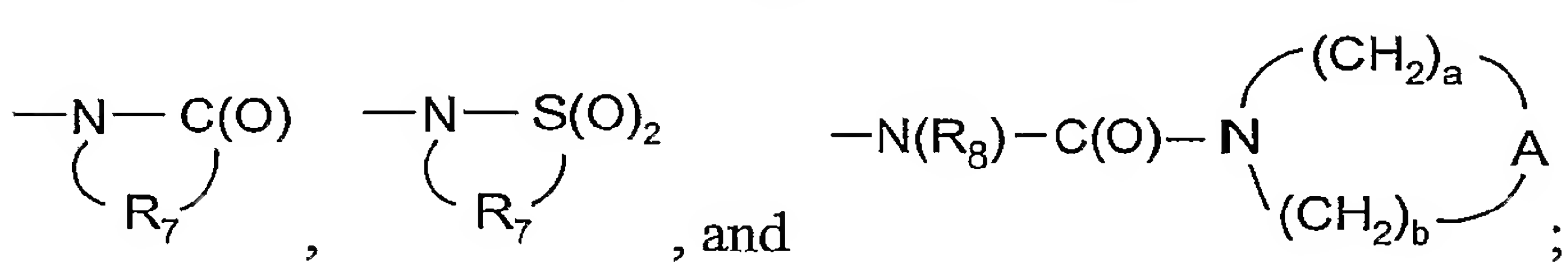
-C(O)-N(R_8)-,

-S(O)$_2$-N(R_8)-, and

-N(R_8)-C(O)-;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, and –N(R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7.

42. The compound or salt of claim 41 wherein R_1 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkynyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl, aryl-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl-O-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-4} alkyl-C(O)-O-C_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl,

aryl-C(O)-NH-C_{1-4} alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-S(O)$_2$-C_{1-4} alkylenyl, amino-S(O)$_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one or two substituents selected from the group consisting of heteroaryl and oxo.

43. The compound or salt of claim 42 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, butyl, pent-4-ynyl, 2-cyclohexylethyl, 2-hydroxy-2-methylpropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-methanesulfonylethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 4-methanesulfonylaminobutyl, 2-methyl-2-[(methylsulfonyl)aminopropyl, 2-(2-propanesulfonylamino)ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-(isobutyrylamino)-2-methylpropyl, 2-methyl-2-(propionylamino)propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-(isobutyrylamino)ethyl, 2-{[(isopropylamino)carbonyl]amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-

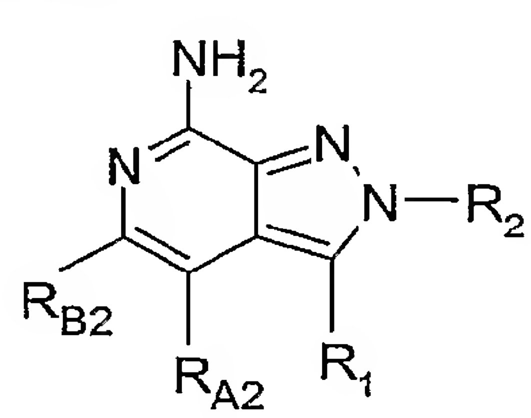
5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

44. The compound or salt of any one of claims 39 through 43 wherein R_2 is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl, and hydroxyalkylenyl.

45. The compound or salt of any one of claims 39 through 43 wherein R_2 is selected from the group consisting of hydrogen, C_{1-5} alkyl, C_{1-4} alkoxyC_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, and arylC_{1-4} alkylenyl wherein aryl is unsubstituted or substituted by one or more substituents selected from the group consisting of chloro, fluoro, methoxy, methyl, cyano, and methoxycarbonyl.

46. The compound or salt of claim 40 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-cyclohexylethyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl; and R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, and 2-hydroxyethyl.

47. A compound of the formula (IX):



IX

wherein:

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$,
$-X-Y-X-Y-R_4$, and
$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,
$-X-R_4$,
$-X-Y-R_4$, and
$-X-R_5$;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
-O-C(O)-O-,
$-N(R_8)-Q-$,
$-C(R_6)-N(R_8)-$,

-O-C(R_6)-N(R_8)-,

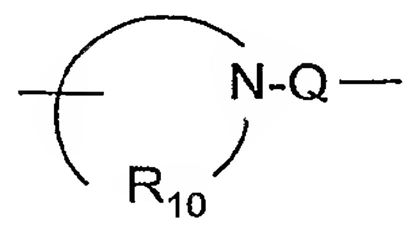
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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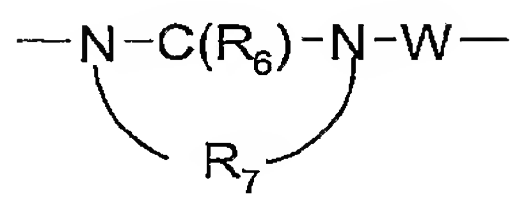

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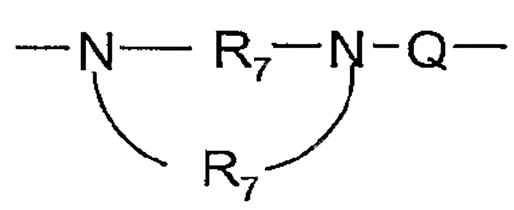

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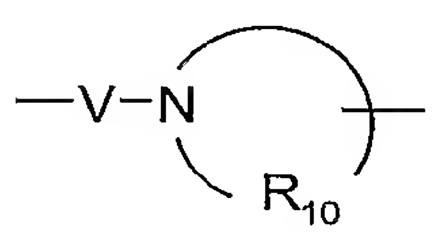

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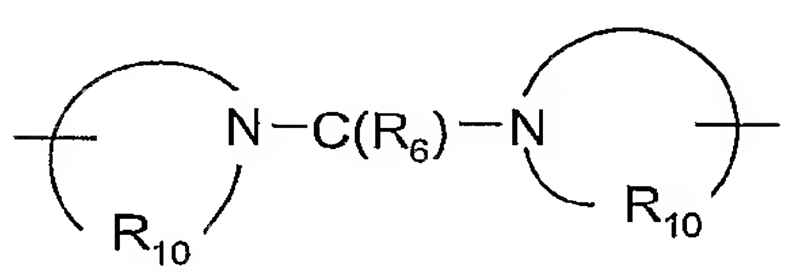
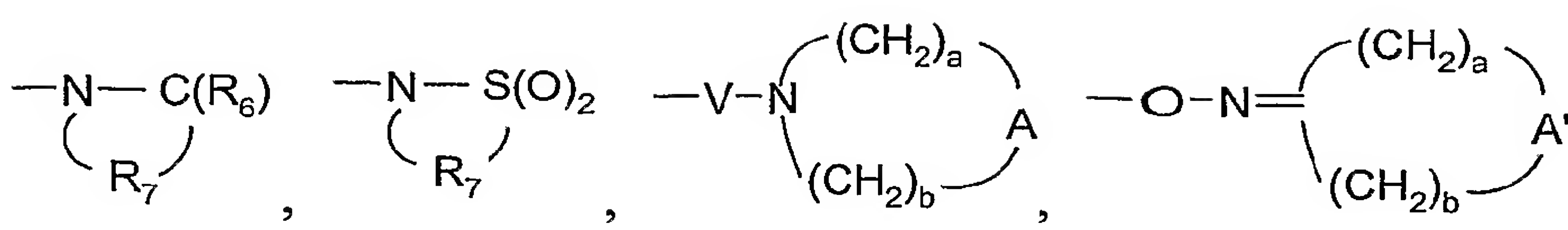


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



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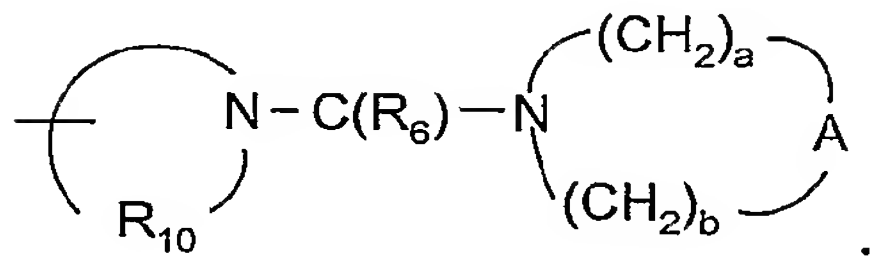


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, and –N(R_4)-;

A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7;

with the proviso that at least one of R_{A2}, R_{B2}, R_1, or R_2 is other than hydrogen;

or a pharmaceutically acceptable salt thereof.

48. The compound or salt of claim 47 wherein R_{A2} and R_{B2} are each alkyl.

49. The compound or salt of claim 47 or 48 wherein R_1 is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X^1-Y^1-R_4, and

-X-R_5; wherein

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted with one -O- group;

Y is selected from the group consisting of:

-O-,

$-S(O)_2-$,

$S(O)_2-N(R_8)-$,

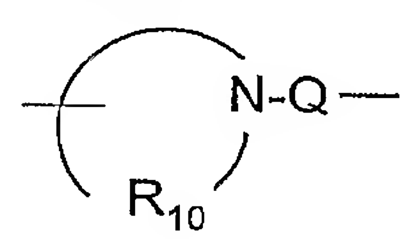
-C(O)-,

-C(O)-O-,

-O-C(O)-,

$-N(R_8)-Q-$,

$-C(O)-N(R_8)-$,



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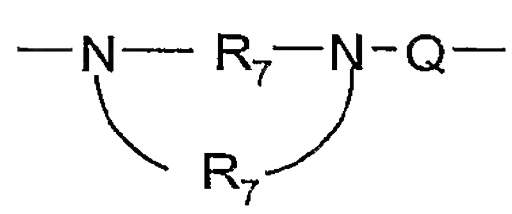


;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of:

-S-,

-C(O)-,

-C(O)-O-,

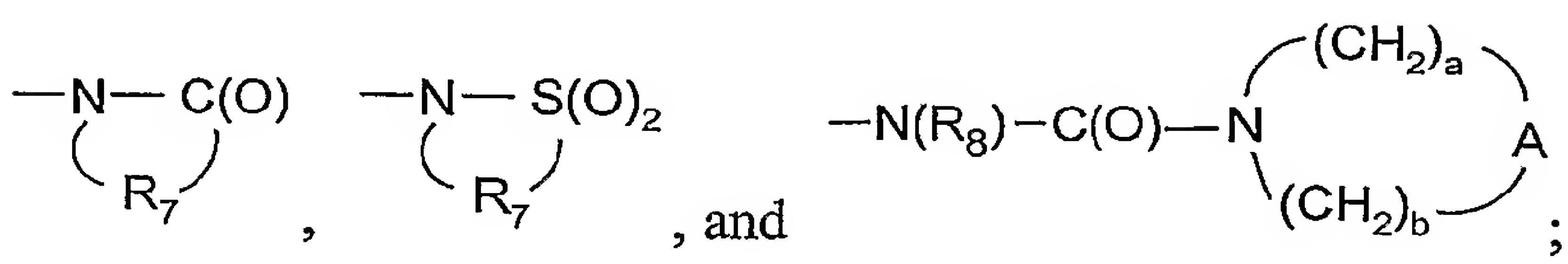
$-C(O)-N(R_8)-$,

$-S(O)_2-N(R_8)-$, and

$-N(R_8)-C(O)-$;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, and –N(R_4)-;

Q is selected from the group consisting of a bond, -C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7.

50. The compound or salt of claim 49 wherein R_1 is selected from the group consisting of C_{1-5} alkyl, C_{2-5} alkynyl, arylC_{1-4} alkylenyl, cycloalkylC_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl, aryl-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-C_{1-4} alkylenyl-O-C_{1-4} alkylenyl, C_{1-4} alkyl-S(O)$_2$-NH-C_{1-4} alkylenyl, hydroxyC_{1-4} alkylenyl, haloC_{1-4} alkylenyl, aminoC_{1-4} alkylenyl, C_{1-4} alkyl-C(O)-O-C_{1-4} alkylenyl, C_{1-6} alkyl-C(O)-NH-C_{1-4} alkylenyl, aryl-C(O)-NH-C_{1-4} alkylenyl wherein aryl is unsubstituted or substituted with one or two halogen groups, heteroaryl-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-S(O)$_2$-NH-C_{1-4} alkylenyl, aryl-NH-C(O)-NH-C_{1-4} alkylenyl, heteroaryl-NH-C(S)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-C(O)-NH-C_{1-4} alkylenyl, C_{1-4} alkylamino-C(O)-NH-C_{1-4} alkylenyl, di(C_{1-4} alkyl)amino-S(O)$_2$-C_{1-4} alkylenyl, C_{1-4} alkylamino-S(O)$_2$-C_{1-4} alkylenyl, amino-S(O)$_2$-C_{1-4} alkylenyl, heteroarylC_{1-4} alkylenyl wherein heteroaryl is unsubstituted or substituted by a substituent selected from the group consisting of aryl, heteroaryl, and alkyl, and heterocyclylC_{1-4} alkylenyl wherein heterocyclyl is unsubstituted or substituted by one or two substituents selected from the group consisting of heteroaryl and oxo.

51. The compound or salt of claim 50 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, 2-methylpropyl, 2,2-dimethylpropyl, butyl, pent-4-ynyl, 2-phenylethyl, 2-hydroxy-2-methylpropyl, 4-hydroxybutyl, 2-amino-2-methylpropyl, 2-aminoethyl, 4-aminobutyl, 2-methanesulfonylethyl, 2-(propylsulfonyl)ethyl, 4-(methylsulfonyl)butyl, 3-(phenylsulfonyl)propyl, 2-methyl-2-[2-(methylsulfonyl)ethoxy]propyl, 4-acetoxybutyl, 4-methanesulfonylaminobutyl, 2-methyl-2-[(methylsulfonyl)aminopropyl, 2-(2-propanesulfonylamino)ethyl, 2-(benzenesulfonylamino)ethyl, 2-(dimethylaminosulfonylamino)ethyl, 4-(aminosulfonyl)butyl, 4-[(methylamino)sulfonyl]butyl, 4-[(dimethylamino)sulfonyl]butyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-[(cyclopropylcarbonyl)amino]-2-methylpropyl, 2-(isobutyrylamino)-2-methylpropyl, 2-methyl-2-(propionylamino)propyl, 2-methyl-2-[(pyridin-3-ylcarbonyl)amino]propyl, 2-methyl-2-[(pyridin-4-ylcarbonyl)amino]propyl, 2-(acetylamino)-2-methylpropyl, 2-(benzoylamino)ethyl, 2-(benzoylamino)-2-methylpropyl, 2-[(4-fluorobenzoyl)amino]-2-methylpropyl, 2-[(3,4-difluorobenzoyl)amino]-2-methylpropyl, 2-[(pyridin-3-ylcarbonyl)amino]ethyl, 2-(isobutyrylamino)ethyl, 2-{[(isopropylamino)carbonyl]amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 4-(4-pyridin-2-ylpiperazin-1-yl)butyl, 3-(3-methylisoxazol-5-yl)propyl, 3-(3-isopropylisoxazol-5-yl)propyl, 3-(3-phenylisoxazol-5-yl)propyl, 3-(3-pyridin-3-ylisoxazol-5-yl)propyl, 4-(3,5,5-trimethyl-1,2,4-oxadiazol-4(5*H*)-yl)butyl, 4-(3-methyl-1-oxa-2,4-diazaspiro[4.4]non-2-en-4-yl)butyl, 2-{[(pyridin-3-ylamino)carbonothioyl]amino}ethyl, 2-{[(dimethylamino)carbonyl]amino}ethyl, and 2-{[(phenylamino)carbonyl]amino}ethyl.

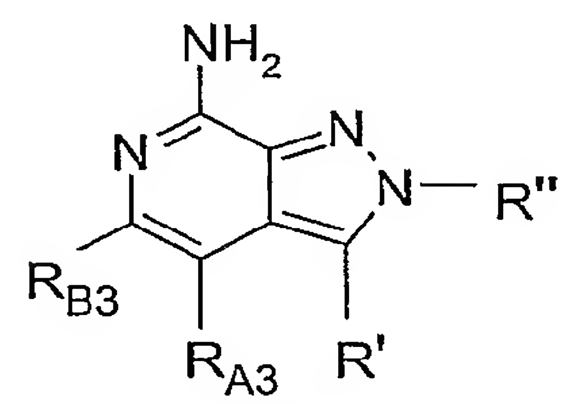
52. The compound or salt of any one of claims 47 through 51 wherein R_2 is selected from the group consisting of hydrogen, alkyl, arylalkylenyl, alkoxyalkylenyl, and hydroxyalkylenyl.

53. The compound or salt of any one of claims 47 through 51 wherein R_2 is selected from the group consisting of hydrogen, C_{1-5} alkyl, C_{1-4} alkoxyC_{1-4} alkylenyl,

hydroxyC_{1-4} alkylenyl, and arylC_{1-4} alkylenyl wherein aryl is unsubstituted or substituted by one or more substituents selected from the group consisting of chloro, fluoro, methoxy, methyl, cyano, and methoxycarbonyl.

54. The compound or salt of claim 48 wherein R_1 is selected from the group consisting of methyl, ethyl, propyl, butyl, 2-methylpropyl, 2,2-dimethylpropyl, 2-cyclohexylethyl, 2-hydroxy-2-methylpropyl, 2-(propylsulfonyl)ethyl, 2-methanesulfonylethyl, 2-methyl-2-[(methylsulfonyl)amino]propyl, 2-[(cyclohexylcarbonyl)amino]-2-methylpropyl, 2-{[(isopropylamino)carbonyl]amino}ethyl, 4-[(morpholin-4-ylcarbonyl)amino]butyl, 2-(benzoylamino)ethyl, and 4-methanesulfonylaminobutyl; R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, 2-methoxyethyl, 2-hydroxyethyl, and benzyl, and R_{A2} and R_{B2} are each methyl.

55. A compound of the formula (Ia):



Ia

wherein:

R_{A3} and R_{B3} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_{A3} and R_{B3} form a fused aryl ring or heteroaryl ring containing one heteroatom or 5 to 7 membered saturated ring optionally containing one heteroatom wherein the heteroatom is selected from the group consisting of N and S and

wherein the aryl, heteroaryl, or 5 to 7 membered saturated ring optionally containing one heteroatom is unsubstituted or substituted by one or more non-interfering substituents;

R' and R" are independently selected from the group consisting of hydrogen and non-interfering substitutents; and

R_9 is selected from the group consisting of hydrogen and alkyl;

with the proviso that at least one of R_{A3}, R_{B3}, R', or R" is other than hydrogen; and with the further proviso that when R_{A3} and R_{B3} form a benzene ring unsubstituted or substituted with chloro, and R' is hydrogen, then R" is other than phenyl or phenyl substituted with methyl, methoxy, chloro, or fluoro;

or a pharmaceutically acceptable salt thereof.

56. The compound or salt of claim 55 wherein R' is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X-Y-R_4, and

-X-R_5; wherein

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

-$S(O)_{0-2}$-,

-$S(O)_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

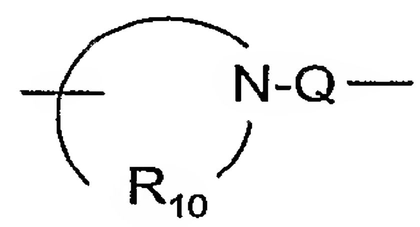
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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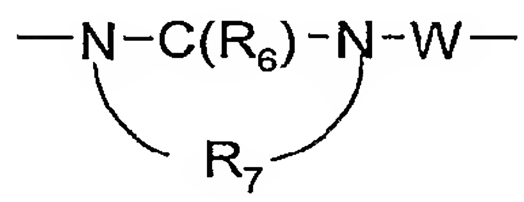

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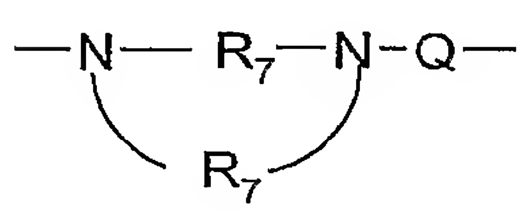

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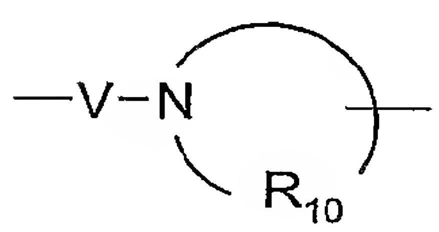

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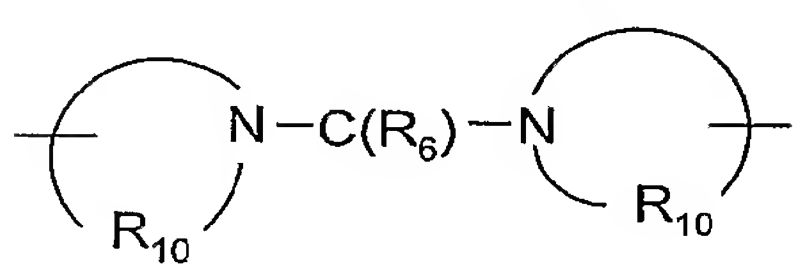
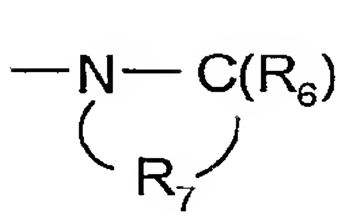
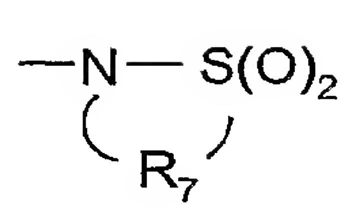
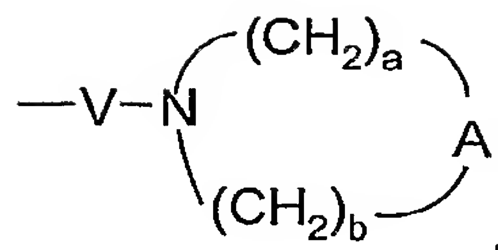
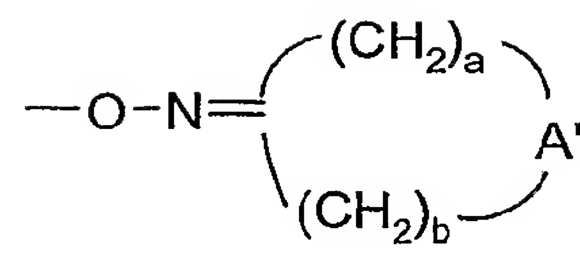
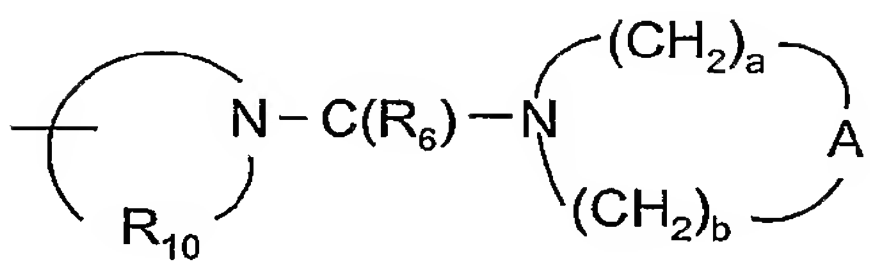


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of

, , , , and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -$S(O)_{0-2}$-, and –N(R_4)-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -$S(O)_2$-, -C(R_6)-N(R_8)-W-, -$S(O)_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

57. The compound or salt of claim 56 wherein R' is selected from the group consisting of:

-R_4,

-X-R_4,

-X-Y-R_4,

-X-Y-X^1-Y^1-R_4, and

-X-R_5; wherein

X is alkylene that is optionally interrupted or terminated by heterocyclylene and optionally interrupted with one -O- group;

Y is selected from the group consisting of:

-O-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,

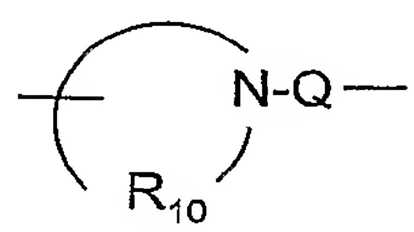
$-C(O)-$,

$-C(O)-O-$,

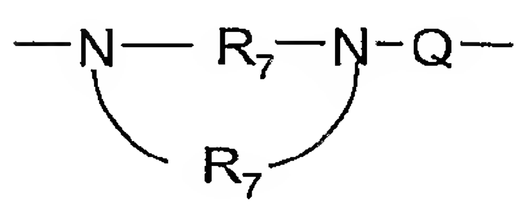
$-O-C(O)-$,

$-N(R_8)-Q-$,

$-C(O)-N(R_8)-$,



, and



;

X^1 is selected from the group consisting of alkylene and arylene;

Y^1 is selected from the group consisting of:

$-S-$,

$-C(O)-$,

$-C(O)-O-$,

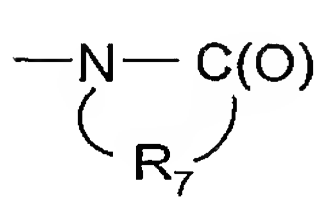
$-C(O)-N(R_8)-$,

$-S(O)_2-N(R_8)-$, and

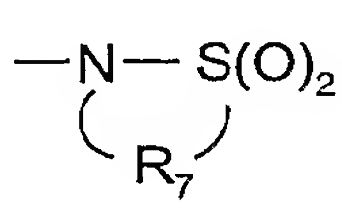
$-N(R_8)-C(O)-$;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkylenyl, alkynyl, arylalkylenyl, and arylalkenylenyl, wherein the alkyl, aryl, arylalkylenyl, heterocyclyl, heteroaryl, and heteroarylalkylenyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, haloalkyl, haloalkoxy, halogen, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, amino, dialkylamino, and in the case of alkyl and heterocyclyl, oxo;

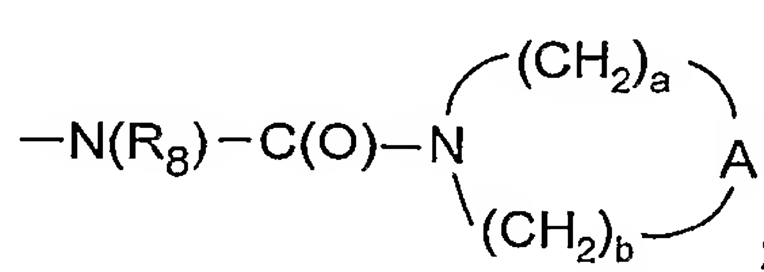
R_5 is selected from the group consisting of:



,



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, and $-N(R_4)$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)$-W-, $-S(O)_2-N(R_8)$-, -C(O)-O-, and -C(O)-S-;

W is selected from the group consisting of a bond and -C(O)-; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7.

58. The compound or salt of any one of claims 55 through 57 wherein R" is selected from the group consisting of

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

$-X-R_5$; wherein

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,

$-S(O)_{0-2}$-,

$-S(O)_2-N(R_8)$-,

$-C(R_6)$-,

$-C(R_6)$-O-,

$-O-C(R_6)$-,

-O-C(O)-O-,

$-N(R_8)$-Q-,

$-C(R_6)-N(R_8)$-,

$-O-C(R_6)-N(R_8)$-,

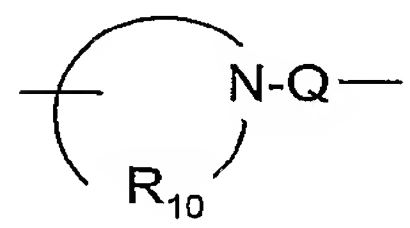
-C(R_6)-N(OR_9)-,

-O-N(R_8)-Q-,

-O-N=C(R_4)-,

-C(=N-O-R_8)-,

-CH(-N(-O-R_8)-Q-R_4)-,



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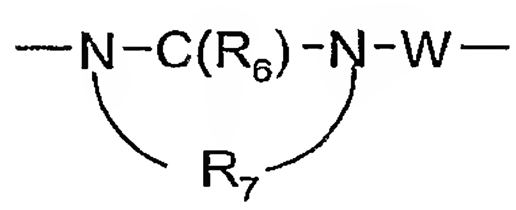

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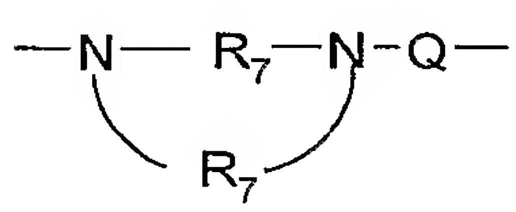

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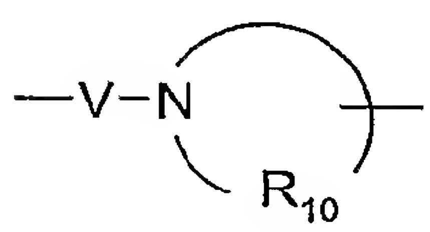

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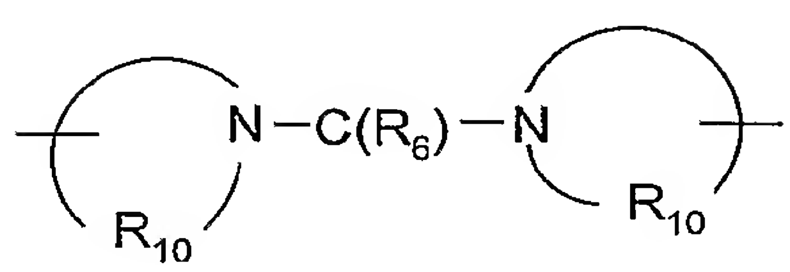
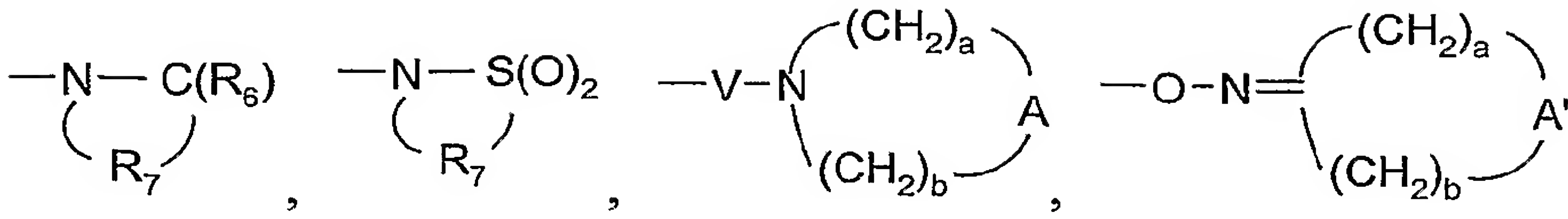


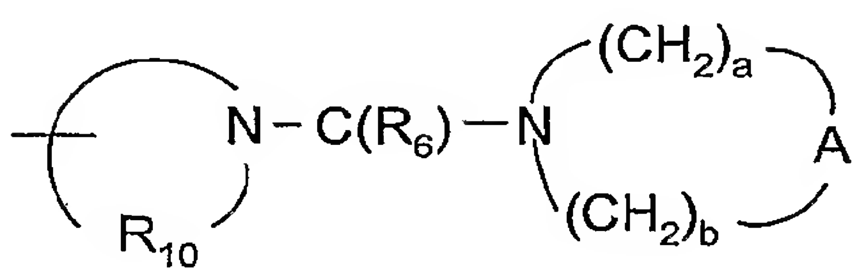
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of



, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, -S(O)$_{0-2}$-, and –N(R_4)-;

A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH$_2$-;

Q is selected from the group consisting of a bond, -C(R_6)-, -C(R_6)-C(R_6)-, -S(O)$_2$-, -C(R_6)-N(R_8)-W-, -S(O)$_2$-N(R_8)-, -C(R_6)-O-, -C(R_6)-S-, and -C(R_6)-N(OR_9)-;

V is selected from the group consisting of -C(R_6)-, -O-C(R_6)-, -N(R_8)-C(R_6)-, and -S(O)$_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –S(O)$_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

59. The compound or salt of claim 58 wherein R" is selected from the group consisting of:

-R_4,

-X-R_4, and

-X-Y-R_4; wherein

X is alkylene that is optionally terminated by arylene or heterocyclylene;

Y is selected from the group consisting of:

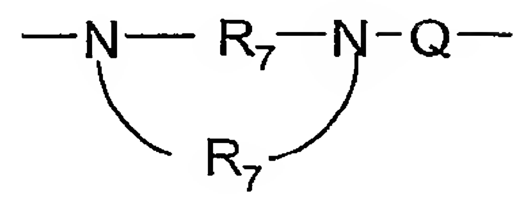
-S(O)$_2$-,

-C(O)-,

-C(O)-O-,

-N(R_8)-Q-,

-C(O)-N(R_8)-, and


;

R_4 is selected from the group consisting of hydrogen, alkyl, aryl, arylalkylenyl, aryloxyalkylenyl, heterocyclyl, and heteroaryl, wherein the alkyl, aryl, aryloxyalkylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, cyano, aryl, aryloxy, heteroaryl, heterocyclyl, and in the case of heterocyclyl, oxo;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, and arylalkylenyl; and

Q is selected from the group consisting of a bond, -C(O)-, -S(O)$_2$-, -C(R_6)-N(R_8)-, and -S(O)$_2$-N(R_8)-.

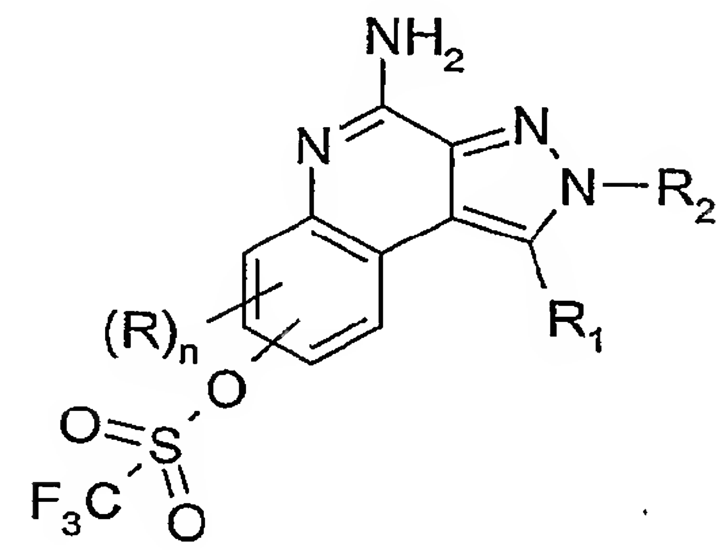
60. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1-59 in combination with a pharmaceutically acceptable carrier.

61. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1-59 to the animal.

62. A method of treating a viral disease in an animal comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1-59 to the animal.

63. A method of treating a neoplastic disease in an animal comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1-59 to the animal.

64. A compound of the following formula (LXXX):



LXXX

wherein:

R is selected from the group consisting of:

halogen,

alkyl,

alkenyl,

trifluoromethyl, and

dialkylamino;

R_1 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$,

$-X-Y-X-Y-R_4$, and

$-X-R_5$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X-R_4$,

$-X-Y-R_4$, and

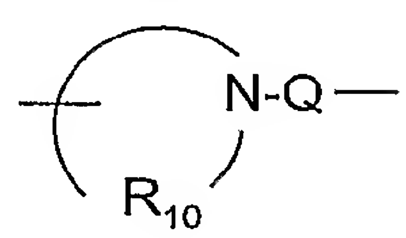
$-X-R_5$;

n is 0 or 1;

X is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-O-,
-S(O)$_{0-2}$-,
-S(O)$_2$-N(R$_8$)-,
-C(R$_6$)-,
-C(R$_6$)-O-,
-O-C(R$_6$)-,
-O-C(O)-O-,
-N(R$_8$)-Q-,
-C(R$_6$)-N(R$_8$)-,
-O-C(R$_6$)-N(R$_8$)-,
-C(R$_6$)-N(OR$_9$)-,
-O-N(R$_8$)-Q-,
-O-N=C(R$_4$)-,
-C(=N-O-R$_8$)-,
-CH(-N(-O-R$_8$)-Q-R$_4$)-,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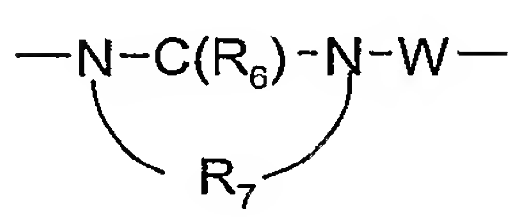
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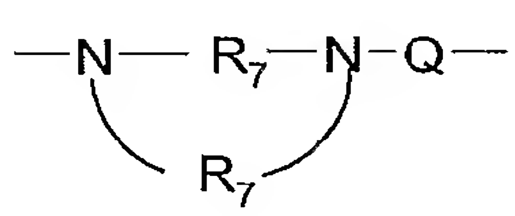
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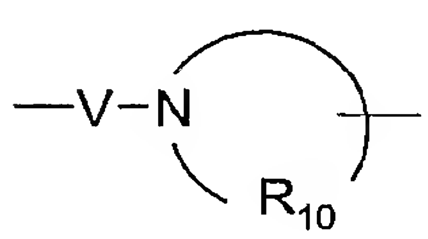
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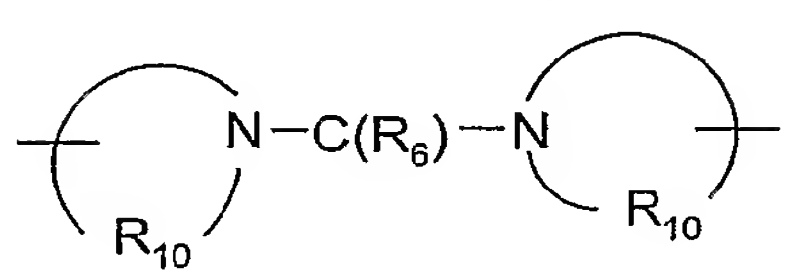
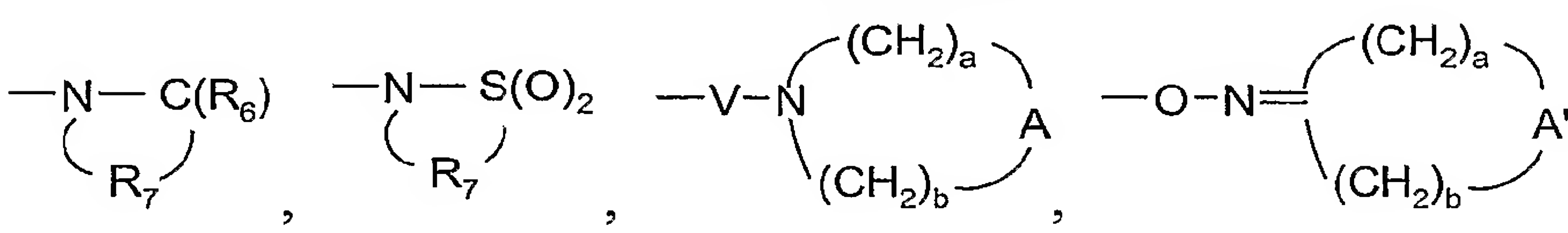
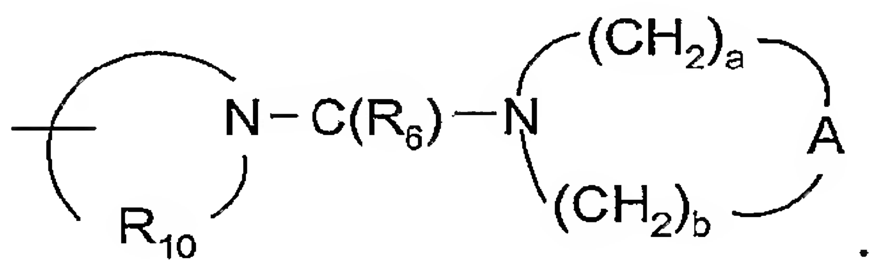

;

R$_4$ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of


, and


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, alkyl, alkoxyalkylenyl, hydroxyalkylenyl, arylalkylenyl, and heteroarylalkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, $-C(R_6)-S-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.